A PLACE FOR HISTAMINE IN NORMAL PHYSIOLOGY *

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UNTIL very recently studies on histamine were mainly concerned with its distribution, liberation, origin, and mode of binding. This " static " approach to the problem, imposed by limitations in available methods, has led to the present impasse in the interpretation of the physiological significance of histamine. A more dynamic approach would place less emphasis on the content than on the rate of formation, the rapidity of turnover, or the rate of " usage " of the amine. In Lund our interest was first turned in this direction by the observation that cats could be starved to the extreme without any concomitant change in the content and distribution of histamine (Haeger and Kahlson 1952). Even removal of the pituitary gland or adrenals did not cause such changes (Haeger, Jacobsohn, and Kahlson 1952). Complete inhibition of the histamine-destroying enzyme histaminase did not influence the tissue content of histamine (Kahlson, Rosengren, and Westling 1958a). We further found evidence of a kind of regulatory mechanism designed to keep constant the tissue level of histamine in the gastrointestinal tract (Haeger, Kahlson, and Westling 1953). All this suggested that the actual tissue content of histamine is a poor indicator of changes in the metabolism of the amine. Consequently we decided to study the spontaneous liberation and rate of formation of histamine under various physiological conditions.

The Origin of Histamine

No methods are available for the accurate estimation of the small changes in the histamine level of blood or plasma which might possibly occur in physiological conditions.

Gaddum (1951) and his colleagues suggested that estimation of histamine in the urine is more likely to give information about the release of histamine in the body than investigations on blood. But this approach is limited by the fact that the food commonly eaten by man and laboratory animals contains substantial amounts of histamine, part of which is excreted in the urine. Further, with such a diet intestinal bacteria decarboxylate histidine to histamine, so adding more exogenous histamine. Large amounts of urinary histamine derived from exogenous sources are likely to conceal increases in urinary histamine derived from increased production or spontaneous release of endogenous histamine.

The complications due to exogenous histamine can be overcome. With two colleagues (Gustafsson, Kahlson, and Rosengren 1957) I investigated the distribution and urinary excretion in germ-free-reared rats fed on a special histamine-free diet, and compared these results with those from ordinary rats fed on the same diet. The distribution and urinary excretion of histamine were largely identical in the two groups of rats, indicating that, when the histamine-free diet is given, the histamine excreted and contained in the tissues is endogenous in origin both in germ-free and normal animals. In the male rat urinary histamine is mainly in the conjugated form. In the female rat, fortunately, the urinary histamine is almost exclusively in the free, biologically active form, which allows assay directly on the isolated ileum of the guineapig. The urinary excretion in what I shall call our " standard rat " thus provides a useful baseline for our studies, and I shall show by further experiments that in this rat the urinary excretion of histamine runs parallel with the rate of formation.

Inhibition of Histamine Formation in Vivo

Until recently no means were known for measuring in vivo the rate of histamine formation. Studies of the urinary histamine in the female rat, measured by the isotopic methods devised by Schayer (1959) have so far proved most useful. (Indeed Schayer's work has contributed decisively to a new era in histamine research.) The isotopic method depends principally on the injection of ^{14}C-histidine and measurement of ^{14}C-histamine and its metabolites excreted in the urine. In the female rat diamine oxidase (histaminase) is the main histamine-destroying enzyme, and aminoguanidine is its specific inhibitor. Under the influence of aminoguanidine a larger proportion of the histamine formed will be excreted in the urine.

Histidine decarboxylase, the enzyme which converts histidine to histamine, can be inhibited in vitro by semicarbazide, but this inhibition is neither very strong nor specific. Miss Rosengren and I have injected our standard rat with semicarbazide in gradually increasing doses, and studied the urinary histamine output over periods of days or weeks. For the first day or two the urinary histamine is lowered, and then, despite the sustained influence of the inhibitor, the original histamine output is restored. When the injections are discontinued, however, the urinary histamine rises far above normal values, suggesting that the enzyme inhibition is overridden by the simultaneous formation of new molecules of histidine decarboxylase. We were able to overcome this " escape " from the influence of the inhibitor by feeding the standard rat on a diet deficient in pyridoxine, a coenzyme of histidine decarboxylase. On this diet semicarbazide in gradually increasing doses reduces the histamine formation to as little as 20% of normal (fig. 1); the animal appeared fairly fit as regards appetite, exercise, and maintenance of body-weight. When semicarbazide is discontinued the striking increase in urinary histamine reflects the overshoot in histamine formation. The histamine content of the skin of the back, abdomen, and ears was examined before and at the time of greatest inhibition of histamine formation. The two sets of figures did not differ, and they show the lack of correlation between content and rate of formation in the skin. This inconsistency can be accounted for by assuming that all binding sites are occupied and that the histamine molecules are held there even when histamine is formed at a very low rate. If this is true, then even a strong histamine inhibitor is unlikely to counteract the adverse effects of histamine liberated in anaphylaxis or allergy. Measures aimed at hindering or tightening the coupling of histamine to the binding sites seems, a priori, more promising as a remedial approach. Cortisone seems to hinder the coupling of histamine to the binding sites (Schayer 1956).

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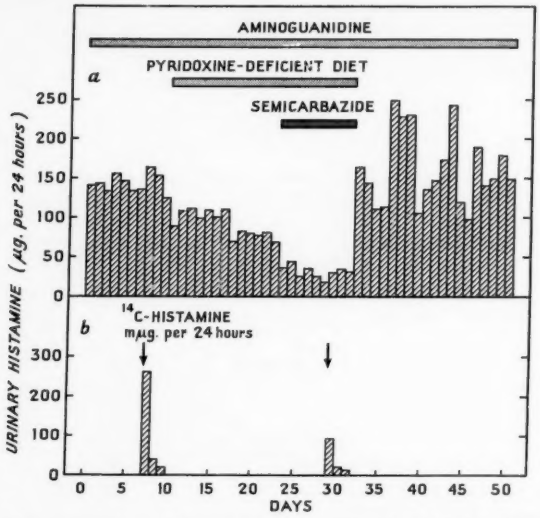

Fig. 1—Female rat fed on a specially compounded histamine-free diet. (*a*) Urinary excretion of free histamine. (*b*) Excretion of ^{14}C-histamine in 0·001 μg. (mμg.) after subcutaneous injection of 220 μg. ^{14}C-histidine (1 mg. per kg.).

Throughout the experiment the rat was under the influence of the histaminase inhibitor aminoguanidine. Pyridoxine was omitted from the diet from the 10th to 32nd day. Semicarbazide was injected subcutaneously on the 23rd to 32nd days (1st day 50 mg. per kg. twice daily, and 2nd day onwards 75 mg. per kg. twice daily).

Antihistamines do not affect the binding sites for histamine, which are different entities from the receptors through which the effects of liberated histamine on smooth muscle and glands are elicited.

Histamine in Pregnancy

Increased Formation of Histamine

The basic observations on histamine formation in pregnancy are represented in fig. 2. In the rat abundant production of histamine starts on the 15th day of pregnancy, as indicated by the rise in urinary excretion. A peak is reached about a day before term, and then, within about 24 hours, the formation of histamine subsides to the prepregnancy level (Kahlson et al. 1958a). If the fœtuses are removed surgically, without interfering with the other products of pregnancy, the rapid histamine formation promptly ceases (Kahlson, Rosengren, Westling, and White 1958b).

To establish which fœtal tissue is responsible for histamine formation, and to assess the rate of production, we incubated various tissues in vitro with radioactive histidine, and measured the ^{14}C-histamine formed. The table shows that the liver produces histamine at an enormously high rate. The histamine-forming capacity per gramme of tissue is about a hundred times higher in the liver than in most other tissues. Even the stomach wall, which in the adult rat is the most potent manufacturer of histamine, is considerably less active per unit weight than the fœtal liver, and a mast-cell tumour of a dog, investigated in our laboratory (Lindell et al. 1959), was about a hundred times less active in forming histamine. In the fœtus about 80% of the total histamine formation takes place in the liver. The day before term the urinary excretion of histamine falls, and within a short time—i.e., 2–3 days—the histidine-decarboxylase activity of the liver regresses from an unparalleled height to the low level found in the newborn and adult animal (see table) (Kahlson, Rosengren, and White 1959).

Absence of Mast Cells and Type of Binding

Mast cells were not found in the fœtal tissues examined except for the skin.

In adult animal tissues, histamine is not easily extracted unless drastic procedures which destroy cell structures are used. In the fœtus the situation is entirely different. The histamine so abundantly formed diffuses freely into the surrounding fluid. When fœtal-tissue suspensions were incubated with ^{14}C-histidine and centrifuged, about 85% of the ^{14}C-histamine formed was in the supernatant fluid. Fœtal tissues bind histamine only loosely, contain little, and produce it at a high rate; hence they are subjected to histamine in a state of rapid turnover (Kahlson et al. 1959).

Histamine Formation in the Human Fœtus

We have investigated the fœtal histamine formation in man and found evidence that it is considerable (Kahlson et al. 1959). Our knowledge of the mechanism is not yet as complete in man as it is in the rat. In human pregnancies terminated on psychiatric grounds, we investigated the histamine content of the maternal and fœtal blood. With the fœtus (weight 90–285 g.) in utero at cæsarean section blood was collected from an umbilical artery. The fœtus was then removed and blood was withdrawn from a carotid artery. Blood was also collected from the umbilical vessels of healthy women at term. Whereas fœtal carotid-artery and umbilical-artery plasma contained histamine in measurable amounts, the maternal plasma did not. The umbilical-vein plasma contained less, and this difference is likely to result from diffusion between fœtal and maternal blood in the placenta.

The Status of Histaminase

The striking increase in histaminolytic activity that can be shown in vitro in plasma from pregnant women is the first and only generally accepted record of a major change in histamine metabolism in normal physiology.

The role of blood histaminase in pregnancy, always obscure, has become even more so on closer examination. Some years

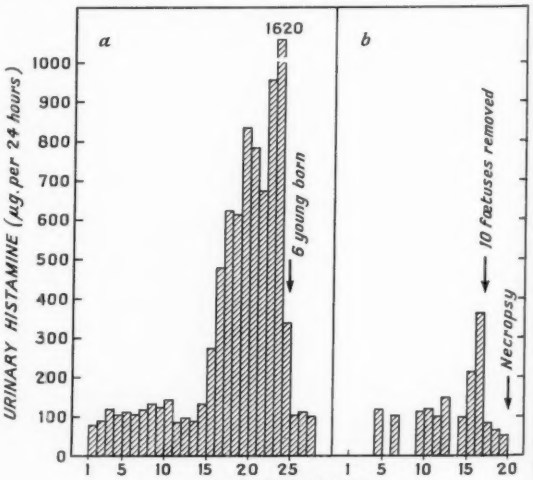

Fig. 2—Urinary excretion of histamine (*a*) in a normal pregnant rat and (*b*) in a rat from which the fœtuses were removed at the 17th day of gestation.

Aminoguanidine was given throughout. (From Kahlson et al. [1958b], by permission of the editorial board of the *Journal of Physiology*.)

THE RATE OF IN-VITRO HISTAMINE FORMATION BY VARIOUS ORGANS OF RAT FŒTUSES (AT THE 19TH AND 21ST DAY OF GESTATION), NEWBORN (WITHIN 3 HOURS OF BIRTH), 2-DAY-OLD YOUNG, AND ADULTS

Tissue	19-day litter	21-day litter	Newborn	Young	Pregnant adult
Total body	..	340	76–970	15	..
Liver	14,000 (*23,000*)	2280	..	5–40	5
Lungs	1900	150	..	5	90–150
Heart	..	140	..	0	..
Kidneys	..	190	..	0	<5
Gastrointestinal tract	..	150	..	..	..
Brain	10	20	..	0	..
"Rest of the body" (muscle, skin, bone)	130 (*220*)	70	..	30	..
Stomach	2800	..	..	..	370–980

The figures represent ^{14}C-histamine formed in 3 hours from ^{14}C-*l*-histidine expressed as counts per min. per g. of tissue. 1 μg. ^{14}C-histamine gives 600 counts per min. The results for the organs were obtained by pooling the tissues in each litter. The figures in parentheses are the mean determinations in three litters. The other figures in the first column are from the same litter.

ago Carlsten and Wood (1951) noticed in cats that transfer of large amounts of histaminase from the kidneys and intestinal mucosa via the lymphatics into the blood-stream, as a result of adrenalectomy, did not cause a measurable increase in blood-histaminase activity. The active enzyme disappeared rapidly from the blood.

Lindell et al. (1958) have reinvestigated, by isotopic methods, the problem of histaminase in human pregnancy. They studied in vivo the metabolism of injected ^{14}C-histamine in pregnant and non-pregnant women. The urinary pattern of the various metabolic products of injected ^{14}C-histamine showed no evidence that histaminase took a substantially greater part in the metabolism of histamine in pregnant than in non-pregnant women. That is to say that the high in-vitro histaminase activity of the placenta and blood-plasma in pregnancy does not contribute in vivo to the inactivation of injected histamine. This finding explains why there is no difference in the sensitivity of pregnant and non-pregnant women to injected histamine judged by the magnitude of the responses so far studied. It should not be taken to indicate that the strong histaminolytic activity in various tissues in vitro represents biochemical or experimental artefacts. For example, it has been shown repeatedly that in our standard rat the urinary excretion of histamine increases two or three times under the influence of the histaminase inhibitor aminoguanidine. The whole problem of histaminase is complex. Studies on histaminase have so far contributed little if anything to our understanding of the physiological significance of histamine, in contrast to what we have learnt from the effect of cholinesterase on acetylcholine.

Resistance in Pregnancy to Histamine-induced Gastric Ulcer

During pregnancy rats are exposed to histamine to an extent which in the non-pregnant animal induces gastric ulcers. An average litter of rat fœtuses produces, towards the end of pregnancy, more histamine in 24 hours than is present in the mother rat. About 2–6 mg. of fœtal histamine enters the maternal rat circulation in 24 hours. A mere fraction of this amount, when mobilised from the non-pregnant animal's own stores by the injection of a histamine liberator, causes ulceration of the glandular part of the stomach (Franco-Browder et al. 1959). Injections of long-acting histamine in beeswax produced ulcers in the stomach and duodenal mucosa in the eight species studied by Hay et al. (1942). Thus pregnancy seems to protect the stomach against histamine-induced ulceration. Clinical colleagues tell me that peptic ulcers are rarely seen and that manifest ulcers tend to heal in pregnant women. The pregnant rat seems to be ideal for studying the way in which the stomach is protected from ulceration. (Incidentally the strong claim for histamine as the final link in the physiological chain of events stimulating acid gastric secretion should be mentioned. Gastrin appears to liberate histamine [Emmelin and Kahlson 1944, Kahlson 1948, Smith 1954]. ^{14}C-histamine, deposited after injection of ^{14}C-histidine, is released in the rat's stomach on feeding [Schayer and Ivy 1957, 1958].) Here we are concerned with non-mast-cell histamine, since these cells are few or absent in the glandular gastric mucosa (Riley and West 1956).

Speculations on the Significance of Increased Histamine Formation

One can do little more than guess the meaning of the rapid histamine formation observed in pregnancy. If we knew of major changes in the rat fœtus at the 15th day of gestation and the day before term (the days of onset and decline of the changes in the histamine-forming capacity) this would give a clue. The smooth muscle of the uterus, which is subjected to mechanical stimulation by distension during the period of rapid growth of the fœtuses, does not contract before term. The uterine muscle seems to be inhibited in some way, and such inhibition may originate from fœtal histamine. This period coincides largely with that of increased histamine formation. In the rat histamine inhibits the smooth muscle of the uterus and may well provide the requisite block. Even the cessation of histamine formation before parturition appears to be appropriately timed. This view is being tested by finding to what extent long-acting histamine in beeswax deposited under the skin postpones parturition.

In no other species so far investigated does histamine inhibit uterine motility. In these species the function of fœtal histamine formation must be different from that in the rat. My colleagues and I thought that histamine formation in the fœtus might somehow be related to the general process of growth, and this idea can be examined.

Histamine and Growth

Histamine Formation in the Regenerating Liver

The growth of the regenerating liver is particularly relevant to our study, because, like fœtal growth, its rate is very rapid. In the rat the median and left lateral lobes of the liver, amounting to about two-thirds in weight, can be removed. This operation has little obvious effect on the rat. The remnant grows and reaches the size of the normal liver within 20 days. The rate of growth is particularly rapid during the first few days after operation (see Harkness 1957).

In partially hepatectomised rats Miss Rosengren and I found that the rate of histamine formation is considerably increased during the phase of liver regeneration. The rate of formation is particularly high during the first week when the growth is rapid. When radioactive histidine was injected, so that histamine was formed, decarboxylation took place faster during liver regeneration than before operation. The rate of histamine formation subsided when the regenerative growth was completed. We found no mast cells in the regenerating liver tissues.

Histamine Formation and Wound Healing

The results on the liver encouraged us to explore the possible involvement of histamine in a third type of growth—namely, wound healing. At our institute a method has been devised by which the tensile strength of healing wounds can be measured. Working with Dr. B. Zederfeldt on rats, we found that repeated injections of the histamine liberator 48/80 considerably increased the tensile strength of healing skin incisions. Since Schayer et al. (1959) demonstrated that 48/80, with

the mobilisation of histamine, causes a great increase in the histidine-decarboxylase activity of rat skin, we have recognised that the augmented tensile strength of the wound may be linked with an accelerated formation of histamine. We have also made measurements in rats in which histamine formation was inhibited by the combination of a pyridoxine-deficient diet and semicarbazide. In these experiments the tensile strength of healing skin incisions was greatly reduced. In the few experiments we have made so far at the time of "overshoot" in the rate of histamine formation after a period of inhibition, the tensile strength has been considerably increased. The connection between histamine formation and constructive metabolism in healing wounds is so close as to be reciprocal. At some later stage of knowledge this relation may be useful in medical practice.

Enzyme Inhibition and Fœtal Development

The chain of evidence associating histamine-forming capacity with the general processes of growth and repair would be complete if one could show that these processes were impaired as a consequence of inhibition of histamine formation. As I stated earlier, no specific inhibitors of histidine decarboxylase are available as yet. But the combination of the inhibitory effects on this enzyme of pyridoxine deficiency and semicarbazide will reduce the rate of histamine formation to a very low level. Miss Rosengren and I have investigated the effect of this type of enzyme inhibition on fœtal development in the rat.

In one group of rats fed on a pyridoxine-deficient diet, semicarbazide was given for 8 days from the 7th day of pregnancy—that is at about the time of implantation of the ovum. On examining the uterine contents at the 19th day (when the weight of a normal fœtus is about 2 g.), the fœtuses were dead, being reduced to a tiny mass of disintegrated material, and the placentæ were small and in a state of regression.

In a second group of rats, also fed on a pyridoxine-deficient diet, semicarbazide was given for 8 days from the 15th day of pregnancy. When the animals were killed on the 22nd day the findings were much the same as in the first group; the fœtuses were dead and mummified, and their growth seemed to have been arrested at about the 17th day—i.e., when enzyme inhibition was greatest. Supporting evidence has been obtained in another group of rats in which injections of the inhibitor were started at the 17th day.

In controls fed on the deficient diet or injected with semicarbazide only no abnormalities in the course of pregnancy and fœtal development were noted (Kahlson and Rosengren 1959).

Thus, after reaching a more advanced stage of development, at about the day before term, fœtal growth seems to depend no longer on a high histamine-forming capacity. As shown in fig. 2 and the table, histamine formation regresses at about 24 hours before term to the non-pregnant level. Accordingly we have found that living young of normal weight are born when enzyme inhibition is instituted during the last days of pregnancy.

Semicarbazide, which is recognised as a carbonyl reacting agent, is known to inhibit a wide variety of enzymes, such as various aminoacid decarboxylases and amine oxidases, among them histaminase. None of the agents whose formation is known to be inhibited by semicarbazide, has so far been found to be specifically related to fœtal development. We have found that complete inhibition of diamine oxidase by aminoguanidine has no effect on the course of pregnancy or the fitness of the newborn (Kahlson et al. 1958a). Further, Dr. G. B. West and Dr. H. Westling have shown that the formation of 5-hydroxytryptamine is not increased in the rat during pregnancy. Lastly, semicarbazide in doses larger than were used in our experiments did not inhibit the endogenous formation of 5-hydroxytryptamine in the guineapig (Weissbach et al. 1957). Thus it seems reasonable to assume that the inhibition of fœtal development caused by semicarbazide is due to inhibition of histidine decarboxylase as shown by the measurable decrease in urinary histamine. Final proof of this assumption will have to await the finding of specific non-toxic inhibitors of histidine decarboxylase. The discovery of a rich source of the enzyme—the fœtal rat liver—is likely to boost the search for a specific inhibitor.

Histamine Metabolism of the Brain

Prof. Geoffrey Harris, Dr. Dora Jacobsohn, and I (1952) showed that the parts of the brain functionally related to the anterior-pituitary gland, the hypothalamus, and the median eminence contained large amounts of histamine, whereas other parts of the brain examined contained very little. My colleague Dr. White (1959), who has now studied in vitro the formation and catabolism of histamine in brain tissue, using Schayer's isotope-dilution technique, finds that the hypothalamus forms histamine much faster than other parts of the brain.

Our findings in 1952 induced Miss Fuche and me to investigate the effect of small "physiological" quantities of histamine on the secretory activity of the anterior-pituitary gland. You will recall that Harris and Jacobsohn (1952), in classical experiments, showed that the anterior-pituitary gland depends for its proper function not on nervous but on vascular connections with those regions in which we found histamine in abundance. Miss Fuche and I (1957) noted in rabbits in which the adrenal medulla had been destroyed that the intravenous infusion of as little as 50 μg. per kg. of histamine caused a significant lymphopenic response which in time, course, and pattern was identical with the response to injected corticotrophin. This response to histamine was absent after hypophysectomy. As a result of this work histamine is included among the possible chemical mediators of the cerebral control of the anterior-pituitary gland. In exploring the physiological functions of histamine we again encounter non-mast-cell histamine. The brain has no mast cells (Riley 1959).

Histamine in Muscular Exercise and Hypoxia

When histamine was brought on the physiological scene, it was thought to be responsible for the vasodilatition of contracting skeletal muscle and for the phenomenon of reactive hyperæmia. Thomas Lewis cautiously introduced the term "H-substance" for this agent. But Anrep, who contributed brilliantly to knowledge in this field by his studies on the nature of urinary histamine (in which he measured the arteriovenous histamine difference in muscles at work and skin in oxygen-lack), claimed identity of the hypothetical H-substance with histamine. After histamine had thus been brought into the limelight, many investigators set out to assess its role in reactive vasodilatation. Much was written on the subject from many parts of the world. In Lund we have worked hard in this field, and I was privileged to study the problem in Cairo under the guidance of the late Professor Anrep. But, despite all this effort, the consensus of current opinion is that histamine has not with certainty been shown to play a part in any of the various kinds of reactive hyperæmia so far investigated.

Oxygen-lack is well known to affect the small blood-vessels directly, dilating them as in reactive hyperæmia, and so it seemed appropriate to examine the output of histamine in this condition. In experiments made in collaboration with Miss Rosengren, our standard rats were exposed to hypoxia in the low-pressure chamber of our subdivision of Aviation Physiology. The chamber was evacuated to a pressure of about 6000 m., with an oxygen content of 45% of that at sea-level. In the chamber the rats showed signs of oxygen-lack. Urine was collected in 24-hour periods. Under the influence of hypoxia the rate of histamine formation was reduced to roughly half of normal. If mobilisation of histamine were concerned in the reactive hyperæmia of oxygen-lack, the reverse should have happened. The experiments so far made are only preliminary and merely show that histamine is in some way involved. We plan to study in greater detail the nature of the underlying changes in histamine metabolism.

Concluding Remarks

To those, like myself, who have been trying to find a simple and clear cause-and-effect relation in which histamine acts as a direct stimulus to and controller of effector cells (such as smooth muscle, blood-vessels, and glands) the present findings may seem bewildering. It now appears, however, that the histamine-forming capacity is in some way connected with the metabolic machinery common to the anabolic processes of development, growth, and repair. The situation is complex and we cannot yet say whether the observed changes in the rate of histamine formation are essential to the events studied or whether they are the outcome of a different primary physiological reaction. In exploring the role of histamine in normal physiology, further work on the inhibition of histamine formation and its consequences in the animal seems particularly promising, especially in relation to fœtal development.

Through the veil two facts emerge with considerable certainty:

1. Histamine, as linked with the physiological events at present being studied, is not formed from mast cells.

2. As far as physiology is concerned, studies of the rate of histamine formation are more promising than the measurement of histamine content.

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CONTROL OF LIPÆMIA IN CHILDREN WITH DIABETES MELLITUS

THE ROLE OF INSULIN AND THE EFFECTS OF A DIET RICH IN UNSATURATED FATTY ACIDS

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IN an earlier publication (Wolff and Salt 1958) it was noted that initially high levels of β-lipoprotein lipid in the serum of untreated diabetic children were rapidly lowered by treatment with insulin. Moreover, in a group of children under good or fair diabetic control, the mean levels of β-lipoprotein lipid, cholesterol, and esterified fatty acid in the serum were higher in patients with blood-sugar levels above 200 mg. per 100 ml. than in those with levels below 200 mg. It was suggested that high levels of certain serum lipids might be at least partly responsible for the early onset of vascular complications in the young diabetic.

In the present study we have attempted to define the effects of insulin on the various serum lipids. Further, in a number of patients already under insulin control, we have studied the diurnal variation of serum lipids to determine how closely blood-sugar and the lipids are related.

In practice, one cannot expect that blood-sugar control will be maintained through the years strictly enough to keep the serum lipids always at a minimum. For this reason we have investigated, in these diabetic children, the effects of a diet rich in unsaturated fatty acid esters.

In a preliminary experiment an emulsion of sunflower-seed oil was given in substitution for some of the animal fat of the ordinary diets. Later, more success was obtained with foodstuffs whose fat was largely composed of corn (maize) oil. When these were given in strict isocaloric exchange with animal fat of the usual diet, certain serum-lipid concentrations were lowered to levels not attainable with insulin alone; and these low levels were maintained even when insulin therapy was somewhat relaxed.

In view of the possible causal relation between elevation of the serum lipids and the early onset of vascular complications in the diabetic patient, these findings may have practical importance.

The Investigation

Our fourteen patients were between the ages of 2 and 14, with diabetes mellitus of varying duration. Four of them, hitherto untreated, were studied to reveal changes in the serum lipids when insulin treatment was first begun. In four already under insulin control diurnal variation of the serum lipids was studied. Eight under insulin control were fed sunflower-seed oil emulsion; five other patients were given a diet containing corn oil.

In preliminary experiments, the usual dietary fat was reduced and a 50% emulsion of sunflower-seed oil in water, suitably flavoured, was given thrice daily. The daily

TABLE I—BLOOD-SUGAR AND SERUM-LIPID LEVELS IN FOUR PREVIOUSLY UNTREATED PATIENTS DURING THE FIRST PHASE OF INSULIN THERAPY

Patient	Hours after insulin therapy begun	Blood-sugar (mg. per 100 ml.)	Serum lipid (mg. per 100 ml.)									
			Cholesterol		Phospho-lipid	Tri-glyceride	Total Esterified fatty acid	Lipoprotein lipid fractions				Total lipid
			Esteri-fied	Unesteri-fied				ω	β	α	Ratio β/α	
A	0	645	110	44	234	412	621	45	1050	185	5·7	1280
	4	376	194	68	264	134	433	66	689	165	4·2	920
	17	302	127	46	143	83	259	65	448	87	5·1	600
	25	60	119	57	169	27	218	91	412	157	2·6	660
	42	498	115	57	200	118	322	73	376	131	2·9	580
B	0	680	210	67	322	158	508	159	529	322	1·6	1010
	16	388	174	67	255	91	373	135	435	290	1·5	860
	42	220	162	57	260	93	373	107	513	260	2·0	880
C	0	578	159	67	311	344	642	104	666	270	2·5	1040
	17	285	121	47	196	129	316	70	365	205	1·8	640
	68	249	134	47	222	184	413	213	394	213	1·8	820
D	0	440	133	65	281	485	738	343	605	172	3·5	1120
	19	304	141	65	216	214	442	233	419	148	2·8	800
	43	416	126	49	203	155	367	131	402	197	2·0	730
Normal range		60–160	85–175	35–75	160–310	0–200	190–450	0–120	300–580	150–280	1·6–3·0	460–860

amount of 50 g. oil contained about 30 g. linoleic acid as the main unsaturated (dienoic) fatty acid.

In later experiments, the diets contained special milk, margarine, and cheese-spread, all made with corn (maize) oil instead of animal fat. Corn oil contains about half its weight of linoleic acid as the main unsaturated fatty acid. The diets were arranged to contain 50 g. corn oil per day for the older children and 40 g. for the younger, as well as known amounts of protein (40 to 60 g.) and carbohydrate (170 to 230 g.) graded according to age. The quantities of corn oil, together with 15 g. other dietary (animal) fat, replaced the total animal fat included in the control diets given before and after the periods of corn-oil feeding. The protein and carbohydrate contents of the corn-oil and control diets were kept constant for each patient throughout the experiments.

In three patients fat-balance studies for periods of 3 days showed normal fat absorption on the corn-oil diet.

Blood-sugar was estimated by the Folin-Wu micro-technique, using unlaked blood in Herbert and Bourne's method (Harrison 1937).

Serum lipoprotein was separated electrophoretically on absorbent paper into ω, β, and α fractions; after staining with oil red O these fractions were estimated on a relative basis by the method described by Salt and Wolff (1957). The fractions were calculated as absolute concentrations by reference to the serum total-lipid concentrations determined by the method of de la Huerga et al. (1953).

Analyses of sera for esterified cholesterol and unesterified cholesterol (Schoenheimer and Sperry 1934), lipid phosphorus (method adapted from Gomori 1942) and total esterified fatty acid (Stern and Shapiro 1953) were also made.

In calculations, a representative molecular weight of 277·2 was used for fatty acid; phospholipid (M.W.806) was obtained by lipid phosphorus ×26; triglyceride was computed by difference calculation.

Results

Effects of Insulin on Hyperlipæmia

Table I shows the effects of insulin on the serum lipids and lipoproteins in four previously untreated patients. They were all conscious on admission; patient A was drowsy and she was the only one who was dehydrated. Ketonuria was present in patients A, B, and D.

Under insulin the high values for serum total-lipid, esterified fatty acid, triglyceride, phospholipid, and β-lipoprotein lipid were lowered to normal within 24 or 48 hours. The α-lipoprotein lipid fraction showed little change; raised β/α ratios decreased rapidly. No uniform change occurred in the serum-cholesterol levels. In three cases these were already normal; in patient B, in whom the concentration was initially high, it was brought down to normal. In patients B and D the initially high ω-fraction became normal.

In patient A the β-lipoprotein was very high at first but the ω fraction was not raised and the serum was optically clear. As the serum-cholesterol and phospholipid values were normal but the triglyceride markedly raised, we conclude that the high β fraction resulted from accumulation within it of triglyceride. In patient C the findings were similar, though the hyperlipæmia was less. In patient D the excess triglyceride was largely in the form of chylomicrons (ω fraction), and the serum was turbid.

The observations suggest that, in these untreated diabetic children, an initial excess of triglyceride was usually and mainly responsible for the hyperlipæmia, and was present either in the β-lipoprotein complex or in the form of chylomicrons (ω fraction). Insulin treatment rapidly lowered the raised triglyceride levels irrespective of whether the excess was in the ω- or β-lipoprotein fractions.

Diurnal Variations in Serum Lipids

We next tried to determine whether there was any relation between blood-sugar levels and any of the serum lipids during a 24-hour period in patients in whom diabetic control had already been established.

Blood specimens were so timed as to avoid postprandial elevations of serum triglyceride. In one patient, blood-sugar and the various serum lipids were estimated at 4 separate times, spaced at intervals between 7 A.M. and midnight, on 4 different days. The widest variation in diurnal blood-sugar observed was from 52 to 384 mg. per 100 ml. On this day, as on the other occasions, the diurnal variation in all the lipid fractions was trivial. In this patient on a later occasion, and in three other patients, comparable observations of blood-sugar and serum-lipid concentrations were made just before and 3 hours after the midday meal.

The results confirmed the diurnal constancy of the lipid levels.

Effects of Unsaturated Fats

Sunflower-seed oil.—The effects of this oil on serum-lipid concentrations were studied in eight diabetic children already under established control with insulin. The first trial extended over 28 days while the patient was in hospital and the unsaturated dietary fat was given in place of an equal amount of the usual (largely animal) dietary fat. Initially the serum lipids were all within the normal range. The effect of the oil feeding, observed at 14 days,

was a lowering of the serum esterified-cholesterol and β-lipoprotein-lipid concentrations. At 28 days the lower levels were maintained.

This patient on a later occasion, and seven others, were fed sunflower-seed oil at home for periods of 22 to 42 days. Under home conditions there was some uncertainty about the maintenance of the diet, and in some patients the insulin dosage had to be increased a little during the trial. These factors may have led to less clear results. However, the serum β-lipoprotein lipid fell in every patient, and the esterified cholesterol fell in most of those whose initial levels were not already low. On a mean basis, serum β-lipoprotein, esterified fatty acid, and phospholipid were lowered to about 80% of the initial levels, esterified cholesterol to about 90%, and triglyceride to about 60%. When sunflower-seed oil feeding was discontinued, all these lipids reverted to previous levels.

Corn oil.—Table II shows the effects of the corn-oil diet on the serum lipids in five patients.

The blood specimens were taken at noon, before the midday meal, so that alimentary lipæmia would not complicate the findings. The ranges and mean values for the serum-lipid concentrations are given only for periods when steady levels had been achieved with the different diets. Analytical values were also recorded for the transition periods but are excluded from the calculations.

In patients B and D the diagnosis had been made recently, and the rapid changes induced by insulin therapy have already been described. In patient E the disease was also of short duration. In all three cases the corn-oil diet was started only after the initial hyperlipæmia had responded to insulin and the various serum lipids had reached steady levels for 1–3 weeks.

Patient F, in whom the diagnosis had been made 2 years previously, was also given the corn-oil diet. In his case evaluation of the data was complicated, because diabetic control was being improved by an increase in insulin dosage during the first control period and shortly before the change to the corn-oil diet. The increased insulin control caused a progressive fall of the blood-sugar, serum-phospholipid, triglyceride, and β-lipoprotein-lipid levels.

Patient G was newly diagnosed and was fed the corn-oil diet from the beginning of insulin therapy; consequently there was no initial control diet period. The values recorded for the corn-oil period (table II) were obtained only when insulin control had become established.

The corn-oil diet reduced esterified cholesterol and β-lipoprotein lipid to about 60% of the initial control levels, total-lipid and esterified fatty acid to about 75%, unesterified cholesterol and phospholipid to about 80%. The α fraction was lowered to about 90% and the β/α ratio to about 65% of the control levels. Serum triglyceride and the ω fraction showed no consistent change.

Two of the patients are being maintained on the corn-oil diet and the results will be reported.

In three patients (E, F, and G) the diet was changed again from corn oil to control. The effects of the isocaloric change are shown in table II. As was expected, a marked rise occurred in all the serum-lipid levels which had been lowered by the corn-oil diet, though at the end of 3 weeks some fractions had not fully regained the levels characteristic of the initial control period.

The detailed effects of the corn-oil diet are shown for patient B in fig. 1. α-lipoprotein lipid increased during the transition period while other serum-lipid levels were falling. Later, when the new equilibrium levels were reached, the α fraction had fallen and reverted to the control level. In patient D similar changes were observed.

Insulin and Corn Oil

In two patients we tried to find out whether the corn oil could prevent the rise of certain serum lipids which is to be expected when diabetic control is allowed to deteriorate.

Fig. 2 shows the results for patient E, in whom insulin dosage was approximately halved for a time. Despite the corn-oil diet, when blood-sugar was elevated there was a definite rise in serum triglyceride, esterified fatty acid, and ω fraction, a slight rise in the β fraction, and a fall in the α fraction. These changes are in the opposite direction to those already described in the previously untreated patient when started on insulin therapy and they were in the same lipid fractions.

Whereas in patient E the insulin dose was decreased abruptly, in the other patient (F) the reduction was more gradual. Similar lipid changes occurred but became

TABLE II—SERUM-LIPID LEVELS IN FIVE PATIENTS UNDER INSULIN CONTROL DURING STEADY STATE PERIODS ON DIFFERENT DIETS. DATA FOR THE TRANSITION PERIODS ARE NOT INCLUDED

Patient	Diet	No. of Observations	Serum-lipid, ranges and means (mg. per 100 ml. serum)									
			Cholesterol		Phospholipid	Triglyceride	Total Esterified fatty acid	Lipoprotein lipid fractions				Total lipid
			Esterified	Unesterified				ω	β	α	Ratio β/α	
B	Control	4	162–191 178	63–74 67	223–292 270	41–108 72	335–405 368	58–139 106	427–555 494	184–226 208	2·03–2·95 2·40	740–920 810
	Corn-oil	2	75–87 81	50–52 51	190–234 212	36–49 43	216–254 235	67–107 87	276–278 277	197–204 201	1·36–1·40 1·38	540–590 565
D	Control	4	123–179 142	49–60 57	220–300 247	15–79 47	243–380 302	71–133 97	285–392 337	202–276 221	1·41–1·69 1·54	620–760 655
	Corn-oil	4	57–79 67	45–60 52	178–260 210	25–55 36	202–236 219	60–128 100	212–262 233	145–240 190	0·88–1·60 1·27	470–580 523
E	Control	2	149–150 150	49–58 54	250–305 278	69–71 70	335–368 352	206–263 235	338–513 426	279–301 290	1·21–1·74 1·48	880–1020 950
	Corn-oil	3	74–92 81	27–49 38	205–231 214	103–211 147	296–398 340	120–229 177	192–259 221	252–288 269	0·67–1·03 0·83	600–740 667
	Control	2	114–123 119	49–53 51	265–313 289	118–169 144	365–452 409	127–184 156	355–379 367	237–278 258	1·28–1·59 1·44	760–800 780
F	Control*	5	108–141 123	32–46 40	203–333 228	62–133 101	305–367 331	22–69 51	344–422 377	180–216 194	1·83–2·28 1·94	580–660 622
	Corn-oil	6	83–105 97	23–37 28	121–184 158	1–64 26	170–246 196	73–114 91	155–313 217	160–206 180	0·75–1·93 1·23	440–560 488
	Control	3	127–155 143	37–48 43	181–210 196	41–119 84	277–322 306	128–276 200	338–368 355	116–171 146	2·15–2·92 2·48	640–735 702
G†	Corn-oil	2	75–75 75	25–25 25	138–150 144	47–67 57	187–211 199	32–70 51	250–255 253	150–153 152	1·67–1·67 1·67	440–470 455
	Control	5	133–155 141	45–58 51	236–255 246	93–167 118	335–429 383	85–155 125	423–547 489	164–248 206	1·70–3·33 2·44	760–900 820

* Blood-sugar levels were high during this period. † No initial control period available (see text).

considerable only when the blood-sugar was allowed to rise to 400 mg. per 100 ml. or more.

In both patients serum cholesterol and phospholipid remained at the low levels characteristic of the response to the diet rich in ur ıturated fats. The slight rise in β-lipoprotein lipid ıs therefore apparently due to an increase in triglyceride contained in the β complex.

Discussion

Consideration of the origin and nature of hyperlipæmia in diabetes raises questions of great importance. Hyperlipæmia undoubtedly exists in the untreated patient; it is promptly moderated by insulin therapy and is induced again in the treated patient if insulin is withheld. In the experiments of Hirsch et al. (1953) the hyperglycæmia induced in diabetics by withholding insulin was accompanied by hyperlipæmia, this consisting mainly in an increase in serum triglyceride. Harris et al. (1953) described a similar abnormality in diabetic acidosis, but also noted that other fractions of the serum lipids were involved in the resultant hyperlipæmia, which in their patients was often further exaggerated by hæmoconcentration.

Wolff and Salt (1958) observed that in diabetic children under established insulin control the mean levels of serum β-lipoprotein lipid, cholesterol, and esterified fatty acid were correlated with the height of the blood-sugar levels.

We are inclined to direct attention to the occurrence of hyperlipæmia in patients whose diabetes, though uncomplicated by ketonuria and acidosis, is not perfectly controlled; and many, if not most patients, fall into this group. Of course hyperlipæmia is likely to be greatest in extreme decontrol with acidosis and ketosis; and we may here recall that juvenile diabetes has a tendency to ketoacidosis.

Strisower et al. (1958) showed by ultracentrifugal fractionation that diabetics in a non-acidotic decontrol phase had mild hyperlipæmia due mainly to an increase in the S_fO-12 lipoprotein class; in diabetics with acidosis there was pronounced hyperlipæmia due to gross increases in lipoproteins of the S_f20-400 classes and this was slightly offset by depletions of the S_fO-12 class and of the high-density lipoproteins. Correlations between ultracentrifugal lipoprotein classes and paper-electrophoresis fractions (Smith 1957) have helped to elucidate these observations.

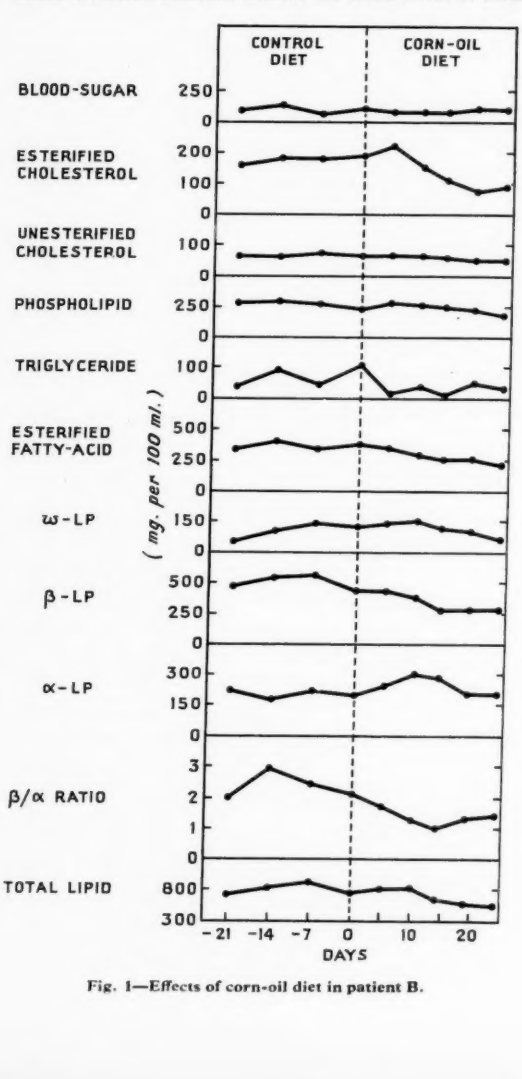

Fig. 1—Effects of corn-oil diet in patient B.

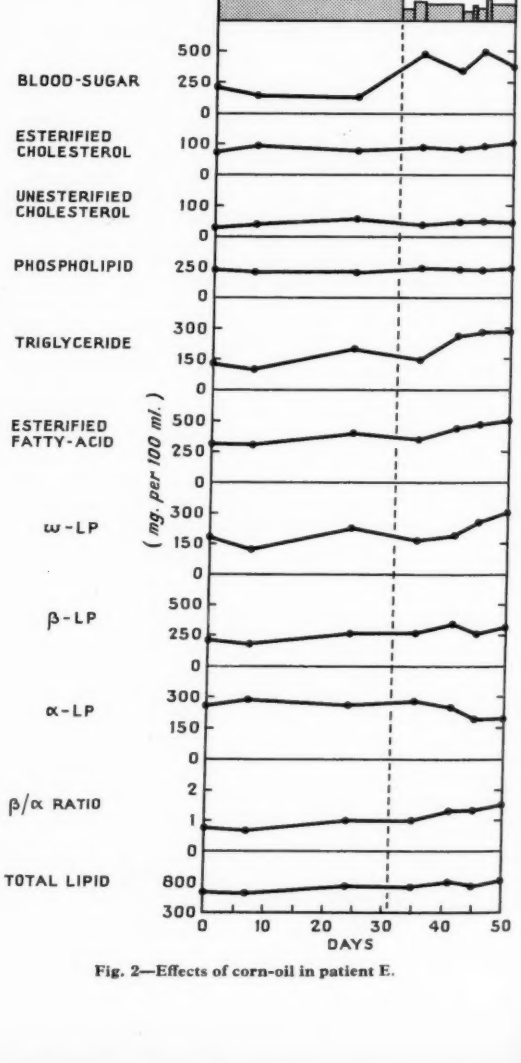

Fig. 2—Effects of corn-oil in patient E.

In discussing the nature and causes of diabetic hyperlipæmia, Albrink and Man (1958) stress the close relation between carbohydrate metabolism and serum-triglyceride concentration. They point out that some excess triglyceride can accumulate in the β-lipoprotein complex, the serum still being clear, but if greater amounts are present they must accumulate in the serum in particulate form. The serum is then turbid. On centrifugation at 18,000 r.p.m. for one hour, a cream-layer (chylomicrons) separates from a clear infranatant solution. We are in agreement with these observations, but have encountered certain sera from hitherto untreated cases in which the infranatant layer was not completely clear. The nature of the material causing the opalescence is under investigation; at present we suspect that it consists of β-lipoprotein containing an excess of triglyceride.

The mechanism responsible for accumulation of triglyceride in the diabetic remains obscure; failure to clear dietary fat is likely to play a part, but endogenous sources are also undoubtedly implicated. Albrink and Man emphasise that with persistent chylomicronæmia there is an associated excess of cholesterol and phospholipid commensurate with the triglyceride. Cholesterol may further accumulate in the β-lipoprotein complex. The excess cholesterol in the diabetic is thought to originate from increased production by synthesis from acetate fragments.

Our present results confirm that hyperlipæmia in diabetic children can be diminished by adequate insulin therapy, the serum triglyceride being mainly affected; and we show that the concentrations of certain serum lipid components, notably β-lipoprotein lipid, can be further diminished by feeding an unsaturated, instead of a saturated, type of dietary fat.

When sunflower-seed oil was fed, serum β-lipoprotein, esterified fatty acid, phospholipid, esterified cholesterol, and triglyceride were lowered. (The lowering of triglyceride may perhaps have been, partly at least, a result of unavoidable increases in insulin dosage.) On the corn-oil diet, serum esterified cholesterol, unesterified cholesterol, phospholipid, esterified fatty acid, and β-lipoprotein lipid were all lowered. Similar results have been reported in adult diabetics from the feeding of safflower-seed oil (Gordon 1957) and of vegetable (nut) oil (Kinsell et al. 1954).

The mechanism by which unsaturated dietary fat lowers the level of serum β-lipoprotein lipid is not clearly understood. Our observations suggest that a transfer of lipid from β- to α-lipoprotein may be an intermediate step, since α-lipoprotein was seen to rise transitorily at the time when β-lipoprotein was being lowered.

In the experiments designed to show the effects of insulin decontrol while the corn-oil diet was being fed, serum triglyceride and esterified fatty acid increased but cholesterol, phospholipid, and β-lipoprotein lipid remained low, showing that the influence of corn oil had persisted. This finding has a special significance for the diabetic in whom the disorder of carbohydrate metabolism, unless constantly well controlled, leads under usual dietary conditions to a rise in cholesterol, phospholipid, and β-lipoprotein lipid levels.

In the young diabetic prevention of vascular disease is the outstanding problem. The lipæmia of diabetes resembles in some respects that known to precede atheroma in older non-diabetic subjects. In both, the β-lipoprotein and cholesterol levels are raised, thus diabetic lipæmia could be a factor in the early development of vascular disease in the young. Though the serum lipids of diabetics can be kept within normal limits by perfect control, the practical difficulties of control are such that it is unlikely to be maintained constantly over long periods. Moreover, excessive insulin dosage must be avoided, because of the risk of hypoglycæmia, suppression of residual endogenous islet function, and development of insulin antagonists. Hence, additional control of lipæmia by dietary means demands a long-term trial.

Summary

In four previously untreated diabetic children, insulin therapy lowered the initially high values for serum triglyceride, β-lipoprotein lipid, esterified fatty acid, and phospholipid to normal within 24 or 48 hours. In one of the patients, in whom the serum-cholesterol level was initially high, insulin brought it down to normal.

In four patients under established diabetic control, observations of the diurnal variations of the various serum lipids and blood-sugar levels revealed a relative constancy of the lipid levels in the face of considerable variation in blood-sugar.

In thirteen diabetic patients under insulin control the effects of feeding unsaturated fats on the serum lipids were observed. Eight were given an emulsion of sunflower-seed oil; this led to a lowering of serum β-lipoprotein lipid, esterified fatty acid, phospholipid, esterified cholesterol, and triglyceride concentrations to levels below the control levels. Five were given a diet in which most of the usual (animal) fat had been replaced by corn oil. The isocaloric change from the control to the corn-oil diet led to a fall in esterified cholesterol and β-lipoprotein lipid to about 60% of the initial control levels, esterified fatty acid to about 75%, and unesterified cholesterol and phospholipid to about 80%.

In two patients on the corn-oil diet the effects of lessening the insulin dosage were observed. The cholesterol and phospholipid remained at low levels, but the diet did not prevent a rise in triglyceride, esterified fatty acid, and the ω (chylomicron) lipid fractions.

The hyperlipæmia of diabetes has similarities to that preceding atheroma in older non-diabetic subjects. It may play an important part in the causation of the vascular complications.

Hyperlipæmia could no doubt be prevented by perfect control of the diabetic process with insulin; but such control, however desirable, is rarely if ever maintained for long periods. As an additional controlling measure, a diet rich in unsaturated fat deserves long-term trial.

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POTENTIATING EFFECT OF QUINOLINES ON THE ACTION OF TETRACYCLINE IN AMŒBIC DYSENTERY

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THE usefulness of antibiotics in the treatment of amœbic dysentery is now widely accepted, and the tetracyclines have been shown to be the most valuable. Tetracycline, chlortetracycline, and oxytetracycline are almost equally effective. In a dosage of 1 g. daily they produced in our hands immediate cure in 92–97% of cases (Elsdon-Dew et al. 1952, Elsdon-Dew 1954–55). Their main disadvantages are expense, failure to prevent hepatic involvement, and a significant relapse-rate. Because of this we have never claimed that tetracyclines can fully replace emetine as the treatment of choice. Nevertheless these antibiotics are of great value for ambulant patients,

TABLE I—RESULTS OF TREATING 50 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE, DIIODOHYDROXYQUINOLINE, AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	12 (24%)	31 (62%)	44 (88%)	47 (94%)	47 (94%)
Probable failure ..	38 (76%)	19 (38%)	6 (12%)	0	0
Parasitic failure ..	0	0	0	3 (6%)	3 (6%)

and we now treat satisfactorily several thousand cases of amœbic dysentery each year as outpatients with tetracyclines together with diiodohydroxyquinoline.

In the following trial our object was to see whether effective treatment could be given at lower costs, with small doses of tetracycline. We also hoped to assess the effect of giving chloroquine and/or diiodohydroxyquinoline in addition.

Material and Methods

Four drug combinations were tested:

1. Fifty patients were treated with tetracycline 50 mg. thrice daily for 10 days, diiodohydroxyquinoline 600 mg. thrice daily

TABLE II—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE AND DIIODOHYDROXYQUINOLINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	6 (24%)	9 (36%)	14 (56%)	15 (60%)	15 (60%)
Probable failure ..	17 (68%)	11 (44%)	5 (20%)	3 (12%)	3 (12%)
Parasitic failure ..	2 (8%)	3 (12%)	1 (4%)	1 (4%)	7 (28%)

for 20 days, and chloroquine sulphate 800 mg. immediately, followed by 400 mg. 6 hours later, and then 200 mg. twice daily for 14 days.

2. Twenty-five patients had tetracycline and diiodohydroxyquinoline in the above dosage, but no chloroquine.

3. Twenty-five patients were given tetracycline and chloroquine in the same dosage as the first group, but no diiodohydroxyquinoline.

4. Twenty-five patients had diiodohydroxyquinoline and chloroquine in the stated dosage, but no tetracycline.

All were African males complaining of diarrhœa with blood and mucus, showing ulceration on sigmoidoscopy, and with actively motile *Entamœba histolytica* in the stools and ulcer scrapings. Severely ill patients, and those with complications of coexisting disease, were excluded.

Sigmoidoscopy was performed on admission and on the 5th, 10th, 20th, and 27th days after starting treatment. Daily stool examinations were performed.

Results were classified into the following categories:

1. *Success.*—Symptom-free, ulcers healed, and no parasites demonstrated.

2. *Probable failure.*—Persistent open ulceration, but no parasites demonstrable in stools or scrapings.

3. *Parasitic failure.*—Amœbæ still present, with or without open ulceration.

TABLE III—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	4 (16%)	8 (32%)	8 (32%)	12 (48%)	12 (48%)
Probable failure ..	15 (60%)	14 (56%)	7 (28%)	1 (4%)	1 (4%)
Parasitic failure ..	6 (24%)	3 (12%)	7 (28%)	2 (8%)	12 (48%)

Cases which remained or became parasitic failures on or after completing their course of treatment under trial were removed at this point and given other treatment.

Results

Tables I-IV indicate that in all groups the majority of patients still had open rectal ulceration at 10 days. Thereafter the ulcers tended to heal. But those who received only diiodohydroxyquinoline and chloroquine (table IV) tended to relapse as soon as their treatment was completed at the end of 20 days, so that by the 27th day only 20% could be classified as successes, and the combined failure-rate was 80%. The group which had tetracycline and diiodohydroxyquinoline (table II) showed only a slightly better success-rate at 27 days (60%, with a combined

TABLE IV—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH DIIODOHYDROXYQUINOLINE AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	6 (24%)	13 (52%)	14 (56%)	5 (20%)	5 (20%)
Probable failure ..	15 (60%)	8 (32%)	8 (32%)	4 (16%)	4 (16%)
Parasitic failure ..	4 (16%)	4 (16%)	3 (12%)	13 (52%)	16 (64%)

failure-rate of 40%) than those who had tetracycline and chloroquine (48%, with a combined failure-rate of 52%). On the other hand the group which received both diiodohydroxyquinoline and chloroquine with tetracycline showed a success-rate at 27 days of 94% and a combined failure-rate of only 6%.

Follow-up Studies

Follow-up was incomplete. But of those patients who received all three drugs three had relapsed within a month, giving a total failure-rate of 12%. Three relapsed in the tetracycline and diiodohydroxyquinoline group, and one in the tetracycline and chloroquine group, giving total

TABLE V—RESULTS OF FOLLOW-UP OF 27-DAY "SUCCESSES" 1 MONTH AFTER DISCHARGE

—	No. of successes available	No. who attended	No. of failures	Total failure-rate
Tetracycline, diiodohydroxyquinoline, and chloroquine ..	47	32 (68%)	3 (6%)	12%
Tetracycline and diiodohydroxyquinoline	15	5 (33%)	3 (20%)	52%
Tetracycline and chloroquine ..	12	6 (50%)	1 (8%)	56%
Diiodohydroxyquinoline and chloroquine	5	3 (60%)	1 (20%)	84%

* The Amœbiasis Research Unit is sponsored by the South African Council for Scientific and Industrial Research, the Natal Provincial Administration, the University of Natal, and the United States Public Health Service (grant E-1592).

failure-rates of 52% and 56% respectively. Of those who had diiodohydroxyquinoline and chloroquine alone one relapsed, giving a total failure-rate of 84%.

Discussion

The use of a systemic amœbicide, such as chloroquine, together with antibiotics, in the treatment of amœbic dysentery is fully justified to prevent hepatic complications. Chloroquine is valuable in hepatic amœbiasis though it has little effect in dysenteric forms of the disease. Our results, however, show a striking increase in the cure-rate when chloroquine and diiodohydroxyquinoline are given in association with suboptimal doses of tetracycline.

Armstrong et al. (1955) found that chlortetracycline in a dosage of 80 mg. daily for 10 days gave a success-rate of 63% at 10 days, but by the 27th day this had fallen to 53%, with a total failure-rate of 47%. In a further series they therefore gave a combination of chlortetracycline 100 mg. daily for 10 days, diiodohydroxyquinoline 600 mg. thrice daily for 20 days, and chloroquine 500 mg. daily for 15 days, and achieved a satisfactory success-rate of 85% at 10 days, and of 91% at 27 days, with a total failure-rate of only 6%. The improved response in this series was ascribed to the addition of diiodohydroxyquinoline, and the possible role of chloroquine was not emphasised.

The results of the present trial lead to surprising conclusions. Earlier trials of diiodohydroxyquinoline gave a success-rate of 58% at 20 days (Armstrong et al. 1949) which corresponds with the success-rate of 56% at 20 days now obtained with diiodohydroxyquinoline and chloroquine combined. In other words, the addition of chloroquine to diiodohydroxyquinoline did not affect the success-rate. Moreover, a high proportion of these patients have now been shown to relapse immediately the drugs are discontinued.

Armstrong et al. (1955) had a success-rate of 53% with small doses of chlortetracycline. We have now shown that the addition of either diiodohydroxyquinoline or chloroquine did not significantly increase the successes. But when the three drugs were used together the proportion of successes rose strikingly to 94%. This seems to indicate that tetracycline in small doses is the most effective drug, but in order to achieve a high proportion of successes the addition of both chloroquine and diiodohydroxyquinoline is necessary. Whenever dysenteric amœbiasis is treated with tetracyclines, therefore, it seems reasonable that chloroquine should be given in addition to diiodohydroxyquinoline not only to safeguard the liver but also because of the enhanced efficacy of combined therapy.

When tetracycline 1 g. daily was given for 10 days the rectal ulcers were healed in 89% of patients by the 10th day, and in 94% by the 15th day (Elsdon-Dew 1954–55). By contrast, when tetracycline 150 mg. daily was given with diiodohydroxyquinoline and chloroquine, the ulcers were healed in only 24% of patients by the 10th day, and in 62% by the 15th day. Thus when tetracycline is used in small doses the rate of healing of ulcers is considerably slower, although the end-result is satisfactory. In view of the slower clinical response and less rapid healing of ulcers tetracycline in small doses is not recommended in acute amœbic dysentery, but it may be justified sometimes where reducing the cost is vital.

Summary

Amœbic dysentery has been treated with four drug combinations:

1. Fifty cases had both chloroquine and diiodohydroxyquinoline in addition to suboptimal doses of tetracycline.

2. Twenty-five cases were given suboptimal doses of tetracycline with diiodohydroxyquinoline.

3. Twenty-five cases had suboptimal doses of tetracycline with chloroquine.

4. Twenty-five cases were given diiodohydroxyquinoline and chloroquine.

Although the addition of either chloroquine or diiodohydroxyquinoline to small doses of tetracycline had little effect, a combination of the two drugs with tetracycline resulted in an immediate cure-rate of 94%. This compares favourably with the results from using tetracycline in the usual dosage, although the ulcers heal more slowly.

We should like to thank Dr. S. Disler, superintendent, King Edward VIII Hospital, Durban, for facilities.

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PSEUDOXANTHOMA ELASTICUM

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DIAGNOSIS depends primarily on the physician's high index of suspicion for certain symptom complexes; this is particularly important in the "rare" diseases, many of which are more prevalent than the sparseness of case-reports would indicate. In this paper I direct attention to the disease known as pseudoxanthoma elasticum (P.X.E.), or the Grönblad-Strandberg syndrome, in which widespread alteration in the elastic tissue produces a characteristic skin appearance, angioid streaking of the retina, and sometimes gastrointestinal bleeding which may be fatal. Every case of hæmatemesis and melæna should be examined for evidence of P.X.E. in order to avoid unnecessary surgical intervention (McKusick 1956). My first patient was recognised thus during systematic examination in the casualty department of the Manchester Royal Infirmary.

Case-reports

Case 1.—A 22-year-old, single, shorthand-typist gave a history of gradually deteriorating vision of her left eye for 6 months. She was otherwise well until 3 days before admission to hospital, when she noticed that she was passing black tarry stools. She was not taking any medicine. On the morning

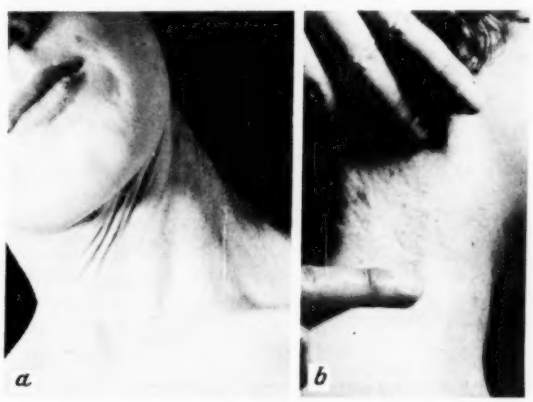

Fig. 1—Case 1: (*a*) redundant folds of skin of the neck; (*b*) coarse-grained appearance of the skin.

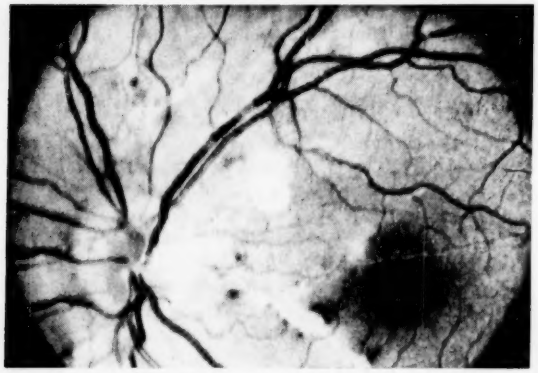

Fig. 2—Case 1. Retinal photograph showing angioid streaks and pigmentation in the region of the macula.

before admission she felt faint and dizzy on running upstairs, and this persisted for 5 minutes. Next day (Nov. 7, 1958) she rose at 5 A.M. to micturate and fainted on standing upright. Later in the day she felt something in her throat, and then vomited a large amount of dark red blood, containing clots. She had no abdominal pain. She had not had any serious illness previously.

Examination

She was slightly distressed. The skin of her neck showed redundant folds and was covered with numerous yellow plaques (fig. 1), some of which had apparently suppurated recently. The skin of the axillæ, antecubital fossæ, and groins was affected similarly; otherwise the limbs were normal. Her mucosæ were pale; there were no buccal lesions. Both optic fundi showed numerous angioid streaks, and the left macula was pigmented (see fig. 2). Visual acuity was J20 in the left eye and J1 in the right eye (uncorrected). The cardiovascular system was normal except for absence of the posterior tibial pulses.

On admission her blood-pressure was 130/80 mm. Hg, and her pulse-rate 120 per minute and regular. The respiratory system and abdomen were normal. The fingers were not clubbed, and there were no spider nævi. Rectal examination was normal apart from melæna.

Gastrointestinal hæmorrhage due to the Grönblad-Strandberg syndrome (P.X.E. with angioid streaks in the retina) was diagnosed.

Further Investigations

A skin-biopsy specimen from the right antecubital fossa was taken on Nov. 11. The histological report was:

The epidermis and superficial quarter or fifth of the dermis shows changes in the elastic fibres; they are greatly increased in bulk, with bulbous or irregular swelling, and extensively fragmented. Von Kossa's method shows widespread calcification of these fibres. An occasional "foreign-body" giant-cell is seen alongside altered elastic fibres; but there is no other cellular reaction. The collagen fibres appear more or less normal; there is perhaps a little focal formation of slender new fibres. The picture is that of P.X.E. (figs. 3a and b).

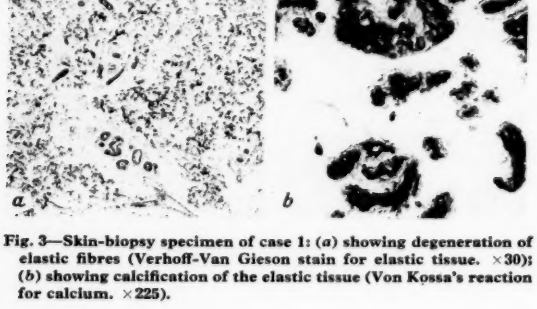

Fig. 3—Skin-biopsy specimen of case 1: (*a*) showing degeneration of elastic fibres (Verhoff-Van Gieson stain for elastic tissue. ×30); (*b*) showing calcification of the elastic tissue (Von Kossa's reaction for calcium. ×225).

An electrocardiogram and a chest radiograph were normal. Radiographs of the lower limbs showed no calcification in muscles or vessels. At barium-meal examination the outline and mucosal patterns of the œsophagus, stomach, and duodenum were normal, and there was no evidence of peptic ulceration.

A full blood-count on Nov. 11 showed: Hb 48% (7·2 g. per 100 ml.), colour-index 1·0, white-cell count 8100 per c.mm. (polymorphonuclears 69·5%, lymphocytes 27%, monocytes 2%, and eosinophils 1·5%), platelets 360,000 per c.mm., and erythrocyte-sedimentation rate (Wintrobe) 10 mm. in the 1st hour. Tests for occult blood in the fæces were strongly positive. Prothrombin activity was 100%.

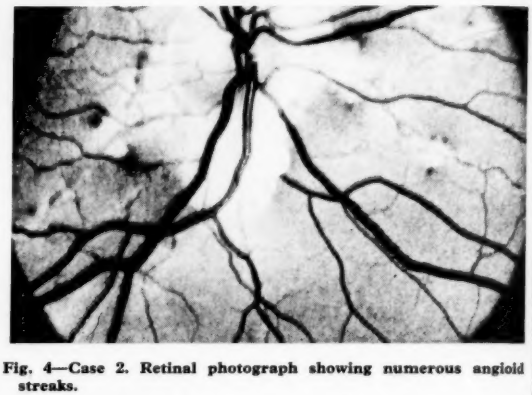

Fig. 4—Case 2. Retinal photograph showing numerous angioid streaks.

Liver-function tests showed: serum-albumin 3·4 g. per 100 ml., globulin 2·6 g. per 100 ml., bilirubin 0·8 mg. per 100 ml., thymol-turbidity 0·8 unit, alkaline phosphatase 6·5 King-Armstrong units, serum-glutamic-oxaloacetic-transaminase 7 units per ml., serum-protein electrophoresis normal, serum-free-cholesterol 45 mg. per 100 ml., ester-cholesterol 140 mg. per 100 ml., and phospholipids 200 mg. per 100 ml. The total fatty acids were 290 mg. per 100 ml., neutral-fat content was 55 mg. per 100 ml., serum-calcium 10 mg. per 100 ml., and serum-inorganic-phosphorus 2·9 mg. per 100 ml.

Progress

The hæmoglobin (Hb) on admission was 56% (8 g. per 100 ml.). She was given a transfusion of 2 pints of whole blood, but next day her Hb had fallen to 38% (5·6 g. per 100 ml.), and she was given a further 10 pints of blood over the next 5 days, while she continued to pass melæna stools. The melæna abated by Nov. 12, when her Hb had risen to 76% (11·4 g. per 100 ml.). Her blood-group was O (rhesus-positive). She was treated at first by a modified Meulengracht regimen. She was discharged symptom-free on Dec. 12, and has remained well. When last seen on Jan. 14, 1959, her Hb was 92% (13·6 g. per 100 ml.).

Family history

All members of the patient's immediate family were examined. Both parents were healthy, with no skin or retinal abnormality and no history of gastrointestinal bleeding or peptic ulceration. A brother, aged 18, was unaffected, but a sister, aged 14, had both skin and retinal manifestations of the Grönblad-Strandberg syndrome (case 2).

Case 2.—This girl had no symptoms. Her skin showed the typical changes of P.X.E. She was normotensive. The retinal appearances were similar to those of her sister—namely, angioid streaks and perimacular pigmentation (fig. 4). She had never had gastrointestinal bleeding. Skin biopsy was not performed, nor, unfortunately, was visual acuity determined.

Discussion

The skin manifestations of P.X.E. were first described in 1884 by Balzer, who classified the disease as one of the xanthomatoses. This was corrected by Darier (1896), who named the syndrome pseudoxanthoma elasticum, and defined the histological changes in the skin. The symptom-complex of skin and retinal changes associated with gastro-intestinal hæmorrhage, failing vision, and weak peripheral pulses in the same patient, was gradually unfolded in several papers over the course of 14 years, starting with Chauffard's description in 1889, followed by Besnier and Doyon (1891), Darier (1896), and finally Hallopeau and Lafitte (1903). The connection between skin and retinal changes was first clearly indicated in the classical papers of Grönblad (1929) and Strandberg (1929), because of which the disease enjoys the eponymous title of the Grönblad-Strandberg syndrome.

Clinical Features

The clinical manifestations of the disease are all dependent on the widespread degeneration of elastic fibres. Collagen itself is not affected directly (Moran and Lansing 1958). The two most striking features are the changes in the skin and retina, but there are less constant manifestations—namely, gastrointestinal hæmorrhage, intermittent claudication, weakness or absence of peripheral pulses by the third decade, dilatation of the aorta, and mental changes.

Skin changes may not appear before the second decade, although in the two cases here reported and in two sisters described by Worringer and Gerhard (1957) the skin changes were noticed in the first decade. The sites of abnormal skin are the neck, axillæ, antecubital areas, inguinal folds, and periumbilical region. The affected skin is coarser and thicker than normal, looking rather like coarse-grained Moroccan leather or a plucked chicken (Szymanski and Caro 1955), the elevations being slightly yellow. The skin is often prone to pyogenic infections; elasticity is lost, and it hangs in redundant folds, particularly in the axillary and inguinal regions. Buccal, rectal, and vaginal changes have been described (Giesen 1936, Carlborg 1944). But the skin may appear normal to the naked eye although histologically abnormal.

Eye changes.—The typical change is angioid streaking of the optic fundus, although this is not always the only finding. Angioid streaks are lines fanning out from the optic disc, which vary in colour from grey to red-brown. They may be due to degeneration of elastic fibres causing cracking of Bruch's membrane, or, as Scholz (1941) suggested, to pigmentation in affected vessels. Angioid streaks may occur also in Paget's disease (Scholz 1941). Other retinal manifestations are macular or perimacular hæmorrhages, colloid bodies (white or yellow discs), and central choroidoretinitis. Blindness may ultimately occur.

Gastrointestinal bleeding.—Massive gastrointestinal hæmorrhage is common (Kaplan and Hartman 1954), and may occasionally be fatal. McKusick (1956) thinks this complication is so important that in all cases of gastro-intestinal hæmorrhage the physician should make a special search for skin changes. Some patients have numerous hæmatemeses before the diagnosis of P.X.E. is established finally. Occasionally the diagnosis is only made on histological examination of the stomach after gastrectomy (Edwards 1958). Often the entire mucosal surface of the stomach oozes blood, there being no discrete bleeding point suitable for surgical attack. Histologically there are often numerous microaneurysms, due to elastic-tissue degeneration in the gastric arteries, with intimal obliterative sclerosis. Four cases of P.X.E. with gastrointestinal hæmorrhage during pregnancy have been described, one of which underwent partial gastrectomy (McCaughay et al. 1956, Woo and Chandler 1958). In view of the increase during pregnancy of factors which relax tissue (Allen et al. 1939), one might speculate that the mechanism of bleeding is a summation of the effect of pregnancy and damage to elastic tissue in the gastrointestinal arteries. Medical treatment seems desirable for patients with P.X.E. and gastrointestinal hæmorrhage rather than surgical exploration, with the almost inevitable sequel of partial gastrectomy, which can be of little benefit when the entire mucosal surface of the stomach is oozing blood. Symptoms of peptic ulceration are unusual. Barium-meal examination rarely demonstrates an ulcer crater (Van Embden Andres 1952). Hæmorrhages from nose, uterus, and bladder, and into the subarachnoid space have been reported; also spontaneous hæmarthroses and purpura, without disturbance of the clotting factors. The peripheral arteries may become calcified due to premature arteriosclerotic changes brought about indirectly by the damaged elastic tissue. This may cause intermittent claudication, with absent or diminished peripheral pulses and peripheral arterial calcification demonstrable radiographically in the legs (McKusick 1956). The arterial degeneration may cause hypertension, intracranial aneurysm, coronary sclerosis with angina pectoris, or aortic aneurysm.

Prognosis

The life prognosis in P.X.E. is good, although patients may die from torrential gastrointestinal bleeding, or from premature coronary atheroma or hypertension. Blindness is common and is often the reason medical advice is sought. The occular complications cannot be treated effectively.

Genetics

P.X.E. is rare in successive generations but multiple involvement in individual sibships is high, indicating that the mode of inheritance is probably recessive. This should give a ratio of affected/unaffected siblings of 1/3, instead of 1/1 as in most reported cases; but this discrepancy may be due to faulty sampling. Remarkably few detailed kinships of P.X.E. have been described, thus precluding adequate statistical investigation of the genetics of the disease.

Touraine (1940a and b, 1941) found that more females than males were affected; of a hundred and sixty-five cases a hundred and four were female. Cockayne (1933) suggested that P.X.E. was partly sex-limited to the female. McKusick (1959) thinks transmission is by an autosomal recessive gene, but he fails to explain the greater prevalence in females. Hermann (1956) concluded that the P.X.E. gene is usually dominant, but admitted that it may occasionally be recessive. Until more case-reports with adequate family histories are published these statements cannot be subjected to adequate statistical analysis.

Summary

Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome) is described in two sisters.

The clinical manifestations are (1) characteristic coarsening and elasticity of the skin due to widespread degeneration of elastic fibres, (2) angioid streaking of the retina causing visual deterioration, and sometimes (3) gastro-intestinal bleeding, which can be fatal.

Genetically the syndrome is probably due to a recessive gene.

In management active but conservative treatment of gastrointestinal bleeding is important.

My thanks are due to Dr. H. T. Howat for permission to publish these cases, and for many valuable suggestions; to Prof. D. A. K. Black for constructive criticism; and to Sir Robert Platt for encouragement and discussion, particularly of the genetic aspects. I am indebted to Prof. A. C. P. Campbell for the biopsy report and the photomicrographs; to Dr. R. G. W. Ollerenshaw of the department of medical illustration for the clinical photographs, and to Dr. P. J. D. Snow for the retinal photographs.

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SALMONELLA OSTEITIS IN NIGERIAN CHILDREN

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SALMONELLA osteitis is a rare clinical entity; by 1950 only nineteen cases had been recorded (Wigh and Thompson 1950). Patients with sickle-cell anæmia, however, seem to be peculiarly susceptible to this complication. Hodges and Holt (1951) first drew attention to the relation between sickle-cell anæmia and salmonella infections, though isolated examples had been reported as early as 1937 (Diggs et al. 1937).

Vandepitte et al. (1953) described five cases of salmonella osteitis seen in patients with sickle-cell anæmia in the Belgian Congo, and mentioned the association. Earlier a greater susceptibility to salmonella infections had been observed among sicklers than non-sicklers in the Belgian Congo (Lambotte-Legrand and Lambotte-Legrand 1951). In 1957 Hook et al. were able to find twenty-nine reported instances, and to add four new cases of their own. In 1958 Roberts and Hilberg described four more cases of salmonella osteitis complicating sickle-cell disease, one of their patients having sickle-cell hæmoglobin-C disease. It has become increasingly apparent that the occurrence of salmonella osteitis and sickle cell anæmia is not merely fortuitous. The *British Medical Journal* (1957) stated: "It seems therefore established that there is a highly significant association between salmonella osteitis and sickling," and drew attention to the possibility, suggested by the Lambotte-Legrands (1951) and Raper (1956), that carriers of the sickle-cell trait might be more liable to salmonella infections than non-sicklers, which would call for reorientation of "our conceptions of the population dynamics of sickling".

TABLE I—SALMONELLA OSTEITIS IN PATIENTS WITH SICKLE-CELL ANÆMIA

Case no.	Age (yr.)	Sex	Site	Bacteriology
1	9	M	Both ulnæ, left radius, both tibiæ	Salmonella isolated from blood; serum agglutinated *S. dublin* (g.p.) 1/1280 and *S. typhi* O (9, 12) 1/320
2	1¼	F	Multiple phalanges, metacarpals, metatarsals, and left radius	Salmonella belonging to group B isolated from pus and stools
3	3	M	Both femora	Salmonella isolated from blood; serum agglutinated *S. typhimurium* H (i) 1/1280
4	¾	M	Left radius, multiple phalanges of feet	Serum agglutinated *S. typhi* O (9, 12) 1/640, *S. enteritidis* H (g.m.) 1/1280, and *S. menston* H (g.s.t.) 1/640
5	1	F	Bilateral metatarsals	*S. dublin* isolated from pus
6	3¼	M	Bilateral radii, ulnæ, and tibiæ	Serum agglutinated *S. paratyphi C* O (6, 7) 1/320, and *S. paratyphi* C H (c) 1/1280
7	1¼	F	Bilateral metatarsals and right ring finger	*S. dublin* isolated from pus; serum agglutinated *S. dublin* H (g.p.) 1/1280, *S. menston* H (g.s.t.) 1/640, and *S. london* O (3, 10) 1/160

The object of this paper is to report thirteen cases of salmonella osteitis seen in the children's department of University College Hospital, Ibadan, between June, 1956, and October, 1958. In seven instances infection was in a proved case of sickle-cell anæmia. One patient was a non-sickler. In the other five patients sickling tests were not performed. One of this group was an 8-day-old infant, and, in view of the known paucity of sickled cells in the blood of the newborn (Watson et al. 1948), it seems highly unlikely that sickling per se was related significantly to the infection.

Clinical Findings

SALMONELLA OSTEITIS IN SICKLE-CELL ANÆMIA

Table I shows the age, sex, sites involved, and bacteriology in seven cases of sickle-cell anæmia complicated by salmonella osteitis. All recovered on chloramphenicol, but in the majority the response was slow, and treatment had to be continued for long periods.

Illustrative Case-report (Case 7)

A Yoruba girl, aged 15 months, presented with painful swelling of the hands and feet of 4 days' duration, associated

TABLE II—SALMONELLA OSTEITIS IN FIVE PATIENTS WHOSE HÆMOGLOBIN GENOTYPES WERE NOT KNOWN, AND IN ONE NON-SICKLER

Case no.	Age	Sex	Site	Bacteriology	Comment
8	3 mos.	F	Left humerus and left scapula	*S. enteritidis* isolated from stools and pus	Anæmia, hepatosplenomegaly; terminal bronchopneumonia; died
9	1 yr.	F	Right femur (lateral condyle)	*S. enteritidis* isolated from pus	Hæmoglobin 60%, general condition good; no hepatosplenomegaly; good recovery
10	8 days	F	? Left femur	*S. enteritidis* isolated from blood	Toxic deeply jaundiced premature infant; died within 12 hours of admission
11	9 mos.	F	Right scapula	*S. chailey* isolated from pus	Not anæmic; good recovery
12	5½ yr.	F	Both tibiæ	*S. ank* ("new species") isolated from pus	
13	14 mos.	F	Right knee, left humerus	*S. saint paul* isolated from pus from both sites	Non-sickler; hæmoglobin 38%; presented with diarrhœa, dehydration, and bronchopneumonia; osteitis apparent 11 days after admission; good recovery

with fever. She was pyrexial and anæmic. There were tender brawny swellings over the dorsum of both feet, and a tender fluctuant swelling over the proximal phalanx of the right ring finger. The liver was palpable. No other abnormality was found clinically.

Special investigations.—Hæmoglobin 6·1 g. per 100 ml.; white blood-cell count 18,800; sickling positive; hæmoglobin electrophoresis showed hæmoglobin S only. Pus aspirated from the ring finger grew *Salmonella dublin* on culture. The serum agglutinated the following:

S. dublin H (g.p.) at 1/1280.
S. menston H (g.s.t.) at 1/640.
S. london O (3, 10) at 1/160.

Radiographs taken when the patient first attended showed changes attributable to sickle-cell anæmia only, but later films showed osteitis of several metatarsals and the proximal phalanx of the right ring finger.

Progress.—The child was treated with chloramphenicol, and the osteitis resolved completely.

SALMONELLA OSTEITIS IN PATIENTS WITH UNKNOWN HÆMOGLOBIN GENOTYPES, AND IN A NON-SICKLER

Table II shows the age, sex, site, salient clinical features, and bacteriology in five cases of salmonella osteitis in which the hæmoglobin genotypes were not known, and in one patient who was a non-sickler. All were treated with chloramphenicol except case 11, which appeared to respond to chlortetracycline.

Discussion

These thirteen cases represent the largest series of salmonella osteitis described to date. Unfortunately, information about erythrocyte sickling is not available in five. Taking into account the many cases of sickle-cell anæmia in the Ibadan area (25% of the population show the sickle-cell trait [Garlick and Barnicot 1957]), some of these are likely to have been cases of sickle-cell anæmia. The clinical findings in one instance (case 8) were highly suggestive of the disease. Our finding seven examples of salmonella osteitis in proven cases of sickle-cell anæmia supports the observation that people with sickle-cell anæmia are peculiarly susceptible to this complication. There can be little doubt that the association is significant.

Figs. 1—Case 1. Salmonella osteitis in sickle-cell anæmia, showing bilateral symmetrical involvement of ulnæ.

Ten of our thirteen cases were seen during the months of July to November. Conclusions about the seasonal incidence of salmonella osteitis cannot be drawn from so small a series, but analysis of the monthly isolations of salmonellæ in Ibadan during 1956 showed a definite peak incidence during the months of June, July, and August (Collard and Sen 1958), when the rainy season is at its height. The observed incidence of osteitis in our cases correlates with Collard and Sen's findings if we allow a time-lag between bowel infection and the onset of osteitis. In five cases we obtained a clear history of diarrhœa preceding the osteitis, and in two, identical strains of salmonellæ were isolated from pus and stools.

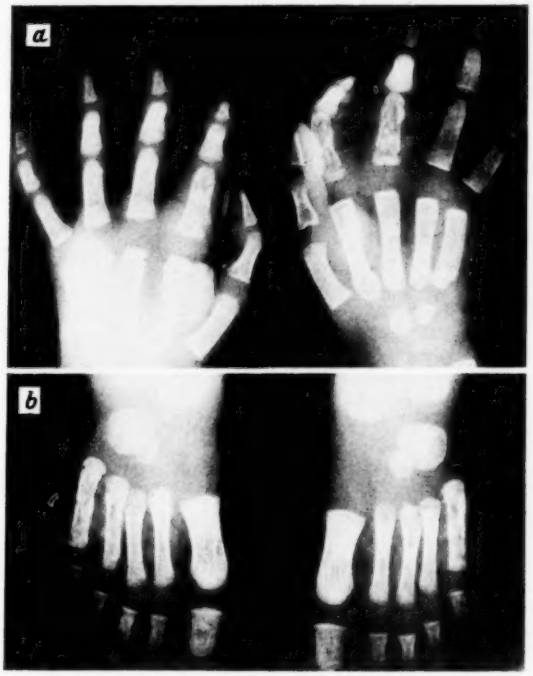

Fig. 2—Case 2. Salmonella osteitis in sickle-cell anæmia involving many bones in hands and feet. Note the symmetrical involvement of the index figures and fifth metatarsals.

In our series salmonella osteitis was most frequent in the first 2 years of life; nine of our thirteen cases fall into this age-group. Other reports also show a higher incidence in this age-group than at any other time (see Hook et al. 1957, Roberts and Hilberg 1958). This finding is probably determined by:

(1) The high incidence of gastrointestinal infections during infancy, especially in underdeveloped areas.

(2) The progressive fall in the number of patients with sickle-cell anæmia seen in successive age-groups. This results mainly from increase in mortality but the observed tendency for the disease to become attenuated with age may be a contributory factor (Lambotte-Legrand and Lambotte-Legrand 1951, 1955, Trowell et al. 1957, Scott et al. 1955, Hendrickse 1959).

Until 1957 reports indicated that males were more often affected than females (3/1), and that *S. paratyphi B* or *S. typhimurium* accounted for 67% of infections (Hook et al. 1957). Our own findings differ. Nine cases were female and four were male, and eight different species of salmonellæ were isolated. The only organism frequently encountered was *S. enteritidis*, which was found in four cases. The majority of the eight types isolated belonged to serotypes associated with an invasive clinical picture.

Sickle-cell anæmia often masquerades as osteitis. These patients are prone to episodes of fever, accompanied by pain and sometimes swelling over bone, associated with leucocytosis and sometimes radiological changes in bone due to infarction. Clinically these episodes are virtually indistinguishable from acute osteomyelitis except by their course and response to treatment. When osteomyelitis does arise, the clinical picture varies very little with different pathogens, except in the response to treatment. In general, salmonella osteitis responds only to chloramphenicol, but even with optimum dosages of this drug response is slow, and relapses tend to follow months or even years after apparent eradication of infection (Hook et al. 1957).

Fig. 3—Case 3. Salmonella osteitis in sickle-cell anæmia, with bilateral symmetrical involvement of femora.

Table I and figs. 1–3 show that multiple sites were affected in all our cases, and that in some the lesions were bilateral and symmetrical. This agrees with other reports (Smith 1953, Vandepitte et al. 1953, Hook et al. 1957, Hughes and Carrol 1957, Wigh and Thompson 1950, Goldenberg 1955). Such a distribution of osteitis is not peculiar to salmonella infections but is seen with other organisms as well. Further, the sites most often affected by osteitis are similar to those most often involved in the spontaneous peripheral manifestations of sickle-cell anæmia. The obvious inference is that areas devitalised by the pathological processes peculiar to the disease become infected by a transient bacteræmia, which in normal persons usually has no serious consequences. Two other factors probably also contribute to the high incidence of salmonella osteitis in sickle-cell anæmia:

(1) Capillary thrombosis consequent on intravascular sickling, which probably decreases the resistance of the gastrointestinal tract to invasion by pathogens, and (2) salmonellæ may remain dormant in bone-marrow for long periods (Vandepitte et al. 1953, Roberts and Hilberg 1958).

Normal people harbouring the organism usually remain symptom-free, though occasionally localised circumscribed areas of osteitis (Brodie's abscess) may arise. In sickle-cell anæmia debility lowers the general resistance to infection, and thrombotic episodes in hæmopoietic tissue and bones lowers local resistance. In these circumstances active infection is to be expected sooner or later in anyone harbouring the organism.

Autosplenectomy in sickle-cell anæmia has been suggested as an additional factor in lowering resistance to infection and predisposing to invasion by salmonellæ (Hook et al. 1957). While the theoretical grounds for this suggestion cannot be contested, most cases of salmonella osteitis reported are of an age where autosplenectomy is rare. Among more than two hundred cases of sickle-cell anæmia under 10 years of age seen in the children's department at University College Hospital, Ibadan, more than 70% had splenomegaly, and autosplenectomy was not observed. Thus in our series autosplenectomy does not seem to be a significant factor in determining salmonella osteitis in sickle-cell anæmia.

Summary

Thirteen cases of salmonella osteitis in Nigerian children are reported. In seven cases salmonella infection complicated sickle-cell anæmia, in five erythrocyte sickling was not looked for, and one patient was a non-sickler.

Our findings suggest a seasonal incidence, and indicate that salmonella osteitis is commonest during the first 2 years of life. Eight strains of salmonellæ were isolated. *Salmonella enteritidis* was found in four cases.

The peculiar susceptibility to salmonella osteitis of persons with sickle-cell anæmia may be due to (1) diminished resistance of the gastrointestinal tract to invasion by pathogens, and (2) diminished resistance to infection in the hæmopoietic tissue and bones. These both result from tissue ischæmia following intrascular sickling and thrombosis. Autosplenectomy is unlikely to have any great significance in determining the incidence.

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INDUCTION OF ANÆSTHESIA IN YOUNG CHILDREN *

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MANY studies of the psychotraumatic aspects of pædiatric surgery and anæsthesia have shown that not all young children survive a stay in hospital unscathed (Gwathmey 1936, Coleman 1950, Albany Research Project 1952, Eckenhoff 1953, Levy 1955, Junkin 1956). The possible causes of psychic trauma (nursing, anæsthesia, surgery, maternal separation) are not segregated easily, though some reports dissociate unjustifiably the induction of anæsthesia from the general adverse effects. Failure to provide suitable sedative premedication is often regarded as a major ætiological factor in late psychic upsets (Slater and Stephen 1951). Unfortunately, therefore, efforts have been directed primarily towards improving premedicant drugs (Slater and Stephen 1951, Rendell 1954, Gusterson 1955, 1957) rather than towards lessening the general psychic trauma of surgery and anæsthesia. Incidentally premedication itself may lead to psychic trauma (Barnes 1952, Ellison 1955, Goulding et al. 1957, Halstead 1955, Rollason 1955, Morton 1957).

* Being part of a paper gaining a research prize awarded by the South West Metropolitan Regional Hospital Board, 1958.

In most children subjected to " everyday " surgical procedures adequate sedative premedication is either contraindicated or impossible. Of nearly nine thousand such children anæsthetised in 1957 in one hospital group, 90% were outpatients or underwent otolaryngeal procedures (Hodges 1959). I believe that failure lies not in lack of premedication but in the way the children are approached and in their reactions to an unpleasant anæsthetic experience.

In a large series of unpremedicated or lightly premedicated children I gained the impression that an anæsthetic technique based on either a single dose of thiopentone, or on thiopentone and nitrous-oxide/oxygen (with suxamethonium where necessary in the longer procedures) lessened some of the untoward sequelæ associated with induction and recovery from the anæsthetic.

Psychiatrists strongly support the belief that neither docile resignation nor an outward calm in the face of disturbing circumstances indicates reliably a child's emotional state. Hence I thought that further study of the true emotional state was necessary before the technique of inducing anæsthesia intravenously in children with little or no premedication is accepted as successful.

The Patients

Children having their tonsils and adenoids out (the most common operation in elective pædiatric surgery) are ideal for studying the psychic trauma of introduction to hospital. In otolaryngeal surgery many think that sedative premedication is contraindicated. These patients, therefore, fulfil the criteria for " everyday " anæsthesia. Their basic reactions to environment and experiences, unmasked by drug sedation, can be studied, providing a baseline for the assessment of premedicant drugs.

A hundred and fifty-five children admitted consecutively for adenotonsillectomy were studied. They were aged from 3 to 12 years, but they mostly fell into the $4^1/_2$–$7^1/_2$ age-groups (fig. 1).

Children with whom one cannot establish contact (usually, though not invariably, the under-3-year age-group) constitute a special problem. Therefore those who could not be approached verbally because of age (three patients), language difficulties (three patients), or congenital maldevelopment (four patients), were excluded from the series. Three children over the age of $10^1/_2$ years were excluded also because in this more mature group the problems are less. Thus a hundred and forty-two children remained in the series.

Method

Admission

24 hours before surgery, the children were admitted to an ear, nose, and throat surgical ward catering exclusively for them. Children in various stages of their hospital stay were intermingled, and, as far as their surgical condition allowed, encouraged to play together. They were screened from the rest of the ward immediately before and after operation, and no new patients were admitted meanwhile. The short-stay routine surgical patients were not visited by their parents.

Preoperative Approach

My practice is to visit these children on the morning of admission. The necessity for a " psychological approach " to children has been stressed often (*British Medical Journal* 1954, Leigh 1949, Collins and Granatelli 1956), and the advantages of intelligent cooperation are obvious.

The technique is not, as many think, time-consuming. These children were treated satisfactorily as a group, and no more than 20 minutes was spent in the essential preoperative examination and explanation. I hold what I call a " pre-anæsthetic class " for the ten to fifteen children scheduled for operation next day, and I think the children find it encouraging to be together. The interviews are informal but disciplined.

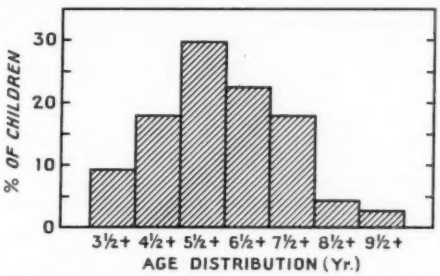

Fig. 1—Age-distribution of the children studied.

The children are asked whether they understand why they are in hospital, and then the preoperative ritual is explained, and, if necessary, demonstrated simply. Questions are encouraged and answered. No promises of freedom from pain or discomfort are made. Once explained, the procedure should be followed implicitly, for it is the unexpected that alarms most. The importance of a truthful explanation cannot be stressed too highly. Most reasonable parents appreciate this, but through their own ignorance they may be unable to explain adequately.

Premedication was by atropine gr. $^1/_{100}$ (0·6 mg.) by hypodermic injection in the early part of the investigation, and by mouth in the later part.

Before operation the children were segregated in a side-room and then taken in turn to the nearby operating-theatre by the theatre porter. Unnecessary people were kept out of the anæsthetic room, and face-masks were not worn.

Induction of Anæsthesia

Thiopentone sodium intravenously was used to induce anæsthesia in all cases but one (case 30). This technique has a particular advantage.

If a child's resolution breaks down during induction he can be calmed and reassured after venepuncture and before injecting thiopentone. In my experience, this has rarely been possible with a child who has become distressed in the initial stages of an inhalation induction.

During the induction of anæsthesia two observers attempted to classify the apprehensiveness of the patient into five grades. Grades 1 and 2 were regarded as successful inductions, grades 4 and 5 as unsuccessful, and grade 3 as intermediate. Variations were recorded in these grades between the time the child entered the anæsthetic room and the establishment of anæsthesia.

Maintenance of Anæsthesia

Anæsthesia for tonsil dissections was maintained with thiopentone intravenously followed by 60–70% nitrous oxide in oxygen through an endotracheal tube, which was passed nasally after suxamethonium had been given intravenously. Small increments of the relaxant were repeated as necessary. No other inhalation agent was used. When the tonsils were guillotined a single dose only of thiopentone was used (Hodges 1955).

After Operation

I make a point of talking with each child as soon as possible after consciousness is regained, and at least once before discharge from hospital, particularly if he has been upset by his experience. Much can be done by way of reassurance at this stage to make future encounters smooth.

The children were given a sedative after operation when necessary (usually an opiate derivative in small doses), and they were kept in bed for 24 hours. They stayed in hospital for about 4 days, depending on the type of operation. The ward-sister was asked to make notes of any abnormal behaviour.

Follow-up

A month after operation I saw the children as outpatients. A questionnaire was sent to the parents of each child after 2–3 months and again after $2^1/_2$ years. With each questionnaire a covering explanatory letter was sent stating the object and

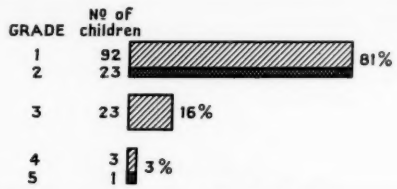

Fig. 2—Grading of apprehension at the time of venepuncture.

aims of the investigation. Finally the results of the first questionnaire were compared with those in a similar series of children who had had anæsthesia induced by inhalation, but who were treated comparably otherwise.

Results

Technique

In three of the hundred and forty-two children venepuncture was difficult, and in one (case 30) it was abandoned. No local complications arose from the intravenous injections.

Apprehension

The gradings at the time of venepuncture represent the greatest apprehension of the children during the period in the anæsthetic room (fig. 2). Though many were successfully upgraded, no child became more apprehensive afterwards (fig. 3). Only three times was a child precipitated from grade 1 to grade 3 by intravenous injection, and then not irretrievably.

These results correspond closely to the clinical impressions gained in many years' study of induction of anæsthesia intravenously.

In the initial clinical assessment of the whole series (table I), there is a suggestion that the younger children are more susceptible to psychic trauma as judged by their reactions during anæsthetic induction. 6% of children under $5^1/_2$ years, compared with 2% of children over this age, had an unsuccessful induction.

Postoperative Course

Immediately after recovery of consciousness I found the children neither difficult to manage nor resentful. No child was persistently distressed, and no abnormality nor behaviour change was obvious in hospital. This impression was confirmed in outpatients later. Only two children were obviously reluctant to return to hospital; one had been told by his parents when brought for admission that " he was NOT going to stay in ", and the other, a 4-year-old, was very dependent on his mother.

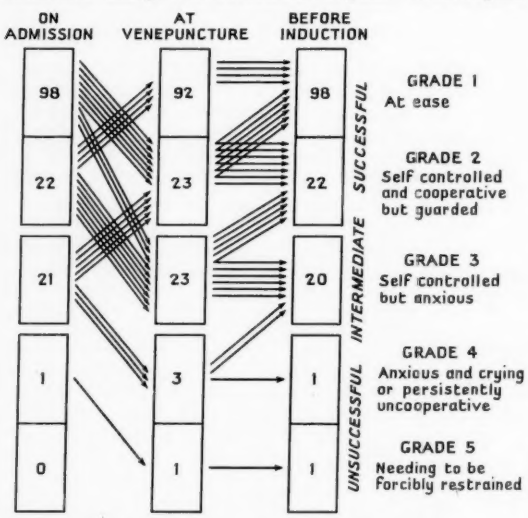

Fig. 3—Grades of apprehension at 3 stages in the anæsthetic room. (The arrows indicate changes.)

Answers to Questionnaires

Detailed replies to the first questionnaire were received from the parents of a hundred and nineteen children—i.e., 84% of the parents circularised. There seemed to be a higher proportion of replies from the group classified clinically as intermediate and failures, than from the more successful cases, but in all other respects there was no difference between the children of those parents who responded to the questionnaire and those who did not.

The replies to the questions are outlined in fig. 4*a* analysed below.

Previous hospital experience.—Nineteen children had had some previous experience of hospital, but, according to the parents, only six (5%) were old enough at the time to appreciate it. Five children had previously had an anæsthetic—all as outpatients—and one of them (case 60) had had two.

TABLE I—CLINICAL ASSESSMENT OF 142 CHILDREN RELATING AGE TO STATE OF APPREHENSION

Age-group (yr.) ..	$3^1/_2$	$4^1/_2$	$5^1/_2$	$6^1/_2$	$7^1/_2$	$8^1/_2$	$9^1/_2$	Total
Total no. of children	9	24	38	36	20	13	2	142
No in each grade:								
Grade 1	4	14	23	27	13	9	2	92
" 2	4	4	6	5	2	2	..	23
" 3	1	4	9	4	3	2	..	23
" 4	..	1	..	..	2	..	..	3
" 5	..	1	..	..	..	..	..	1
No. with failed (group 4–5) inductions ..	0	2 (8%)	0	0	2 (10%)	0	0	4 (3%)
	6%		2%					

Reasons given for hospital admission.—The reasons supplied by the parents to their children were classified as adequate, when a simple truthful explanation had been given, or inadequate, when the explanation might have led the child to expect something different from what was to happen. Explanations based on the necessity to cure some chronic symptom of which the child was quite aware, but without details of what would happen, were also considered adequate—e.g., " to cure those coughs and earache ". Obviously inadequate explanations included such fantasies as " like going to fairyland ", or " like a holiday from school ", and such deliberate deceptions as " the doctors are only going to look ", or " you're not going to stay in ". Explanations were also classified as inadequate when the treatment was allegedly to improve some vague condition in which the child had no interest or of which he might be unaware—e.g., " to stop you snoring ", or " because your tonsils are too big ". Sometimes it was impossible to decide whether or not the explanation offered was adequate, but nine children (8%) had been given an obviously inadequate explanation.

What did your child think of his or her stay in hospital?—The parents of 75% of the children said that their child was contented and happy in hospital. Many children were enthusiastic, often using expressions such as " I enjoyed it " (forty-nine children), " I wish I could have stayed " (four children), or " it was very nice ". 18% of the children expressed no adverse comment but had no particular liking for their experiences. Only 7% commented adversely. Two children were " not keen "—one because of homesickness. Two were " disappointed ". Two were " rather unhappy "—one because of fear of smells and injections (case 30) and one because of homesickness. Two children who gave an unqualified " did not like it " were a 9-year-old delinquent boy and a wayward 8-year-old girl.

Comparison with previous experiences.—In the few cases where this question applied no significant information was gathered.

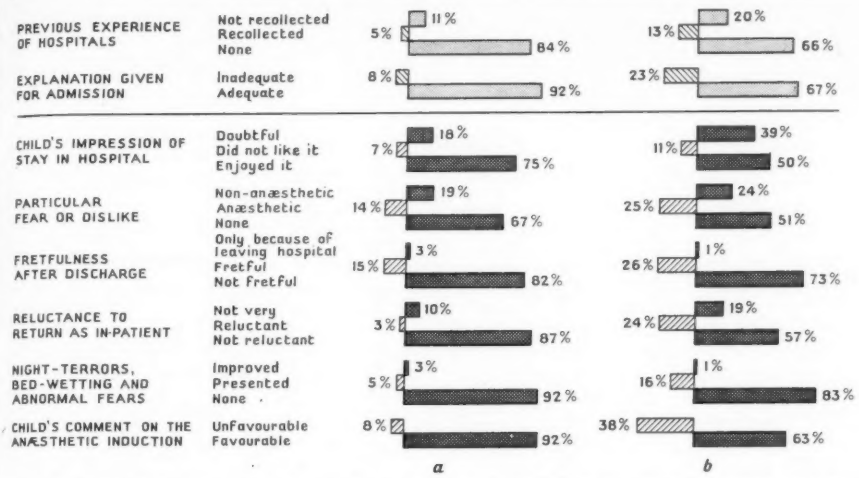

Fig. 4—Replies to the questionnaires: (*a*) anæsthesia induced intravenously; (*b*) anæsthesia induced by inhalation.

Was there anything that the child particularly disliked or would be frightened of in the future?—Seventy-nine children (66%) had expressed no particular fear or dislike. Forty children had dislikes, but in twenty-three they were not associated with the anæsthetic. These dislikes were minor and insignificant (mouthwashes, food, nightclothes, toys, cots) with the exception of two children who were homesick. Nineteen children had fears which could not be dissociated from anæsthesia. Two were frightened of the hospital " atmosphere ", smells, equipment, &c. In case 60 this fear was related to the previous admissions to hospital; he was consequently only reluctant to return to the previous hospital. Three other children were reluctant to return to hospital, and these together with twelve others (13%) " disliked " injections, but in only one child (case 30) did this amount to fear. Seven were referring to their premedication hypodermic atropine and not to the intravenous injection. (Because in the early part of the investigation several children found the atropine injection was their most unpleasant experience, the premedication was later given by mouth.)

TABLE II—RESULTS OF SECOND QUESTIONNAIRE

Question	Answer	No. of children
Does child talk of hospital now?	When reminded or asked	6
	Still mentions " smells "	1•
	Only to comfort others	1
	Only lightheartedly	1
	Does not want to return	1
	Never mentions it	8
Was child permanently upset?	Not permanently	2
	Not at all	16
Did behaviour change persist?	No	17
	Recent tantrums	1
Has child been to hospital since?	No	16
	Yes	2
Did child go quite willingly?	Not applicable	16
	Yes	2

• This child was anæsthetised by an inhalation technique (case 30).

Was your child fretful after leaving hospital?—Three mothers replied, in effect, " only because he didn't want to come home ". Eighteen others (15%) were fretful after leaving hospital, but in only one child (case 60) was this more than slight and transient.

Would your child be reluctant to become an inpatient again, and why?—The parents of a hundred and four children (87%) said " no " dogmatically. Twelve (10%) said " Not very, but . . .". Three of these children had been homesick, one was fearful of the hospital " atmosphere ", and eight showed reluctance for unspecified reasons. Only three children were extremely reluctant to return. Two of these were below school age and homesick, and one (case 30) was frightened of needles.

Behaviour changes.—A hundred and four children showed no change in behaviour and in four children previous behaviour difficulties were improved. In eleven children changes of some sort appeared for the first time, or an established difficulty became worse. Minor fears—e.g., of smells and strangers—arose in five patients and severe night terrors in six (5%).

Did your child make any comment on how he or she was put to sleep for the operation?—A hundred and ten children (92%) made favourable or non-commital remarks—e.g., " just a prick ", " it didn't hurt a bit ", " I didn't mind ", " it was wonderful ", &c. Of the five children who had previously had an anæsthetic three said that it was " better than the mask ", one (case 60) " did not like the smell " (a reply which may have been related to the previous experience), and the other said he would " rather have a balloon ". The parents of nine children (8%) gave unfavourable replies, in eight cases because of the injection.

Other comments included a mixture of helpful suggestions, minor criticisms, and thanks, which were not strictly relevant to this paper.

The replies to the second questionnaire were either entirely negative or were a recapitulation of the facts already known. In none of the eleven patients had the previously reported behaviour change persisted. The replies from the parents of these and eleven other children in whom at the final assessment there was reason to doubt the success of the technique are listed in table II).

Classification of Findings

The children can be divided into two groups. In group 1 all psychic trauma had been avoided, but in group 2 it had not (see table III).

The children in group 1 showed no fretfulness nor behaviour changes after operation, and their parents thought they would submit willingly to a similar procedure. Ninety-seven children (82%) fall into this category as judged by the results of the first questionnaire. These included eighty-one of the ninety-five children in whom anæsthesia had been induced successfully on clinical grounds, thirteen of the twenty-one classified as intermediate, and all those classified as failures. In none of the children with clinically successful inductions who ulti-

TABLE III—CLASSIFICATION OF 119 CASES FOLLOWED-UP FOR 2½ YEARS AFTER OPERATION

Grade of state of apprehension at induction	1 and 2	3	4 and 5	Total
Group 1 (successful): No fretfulness, no behaviour change, would be willing to submit to similar procedure again . .	81	13	3	97
Group 2a (successful): Same as group 1, but fretful postoperatively	8	3	..	11
Group 2b (unsuccessful): Children with postoperative behaviour changes:				
Minor	3	2	..	11
Major	3	3	..	
Total	95	21	3	119

mately showed psychic trauma could anæsthesia be incriminated. Thus clinical assessment seems to be a fairly reliable though possibly pessimistic guide to the success of anæsthetic induction.

Most of the children (eighty-eight) in group 1 made no adverse comment on the induction of anæsthesia, but nine confessed to a dislike of "needles". Seventy-seven admitted to no dislike or fear, but eighteen had a minor dislike of some sort which was not related to the anæsthetic, and one child mentioned homesickness.

The general impression gained was that, far from being harmed, most of the children in group 1 had benefited from their stay in hospital. The experience was of a maturing nature. The parents said, for example, "it made her feel quite grown-up, and she loved helping the nurses" or "it was an enjoyable adventure, something to boast about". Even children who appear distressed when anæsthesia is induced, and who may show reluctance to return to hospital, have probably not undergone psychic trauma provided that they show no specific fear and no behaviour changes after operation.

The children in group 2 are more difficult to assess. In 27% of cases (compared with 8% throughout the whole series) the parents had given inadequate explanations of the reason for admission. The second questionnaire was completed by 82% of the parents of these children (table II).

TABLE IV—THE PROBABLE CAUSE OF PSYCHIC TRAUMA IN CHILDREN WITH POSTOPERATIVE BEHAVIOUR CHANGES

Case no.	Age (yr. & mo.)	Particular dislike	Reluctance to return	Induction comment	Behaviour change	Cause of psychic trauma
68	7⁴/₁₂	+	+	?	Fear of smells	Hospital "atmosphere"
78	6		+		Fear of strangers	Maternal separation
119	4¹/₁₂		+		,,	,,
94	7⁷/₁₂	+ (anæsthetic)			,,	Anæsthetic
147*	4⁶/₁₂		+++		,, and smells	Parental deceit
85	7¹/₁₂	+	+		Night terrors	Maternal separation
76	7¹/₁₂	+	+		,,	Inadequate parental preparation
43*	5¹⁰/₁₂				,,	Maternal separation
143	4	+	+		,,	,,
148	4⁶/₁₂	+ (anæsthetic)			,,	Anæsthetic
11	6⁸/₁₂	+ (anæsthetic)	+	+	,,	,,

* Did not reply to the second questionnaire.

Within group 2 the children can be divided into two categories. Those in the first category may have had some shortlived minor upset (e.g., homesickness, dislike of injections, or discontent) as signified by their transient fretfulness; but, as none of these children had any other behaviour change, their management can probably be regarded as successful. In the second category the children all showed behaviour changes, and their management cannot be regarded as successful. The psychic trauma which caused minor behaviour changes was attributable to the anæsthetic in only one case, but in two children with major behaviour changes anæsthesia was probably responsible (table IV).

TABLE V—RELATION OF AGE TO FINAL ASSESSMENT IN CASES WHICH WERE NOT CONVINCINGLY SUCCESSFUL

Age-group (yr.) ..	3¹/₂+	4¹/₂+	5¹/₂+	6¹/₂+	7¹/₂+	8¹/₂+	9¹/₂+
No. in final classification:							
Group 2a	1	1	3	4	2	..	..
Group 2b	2	2	3	2	2	..	..
Percentage of each age-group	33%	13%	16%	17%	20%	0	0
	18%		15%				

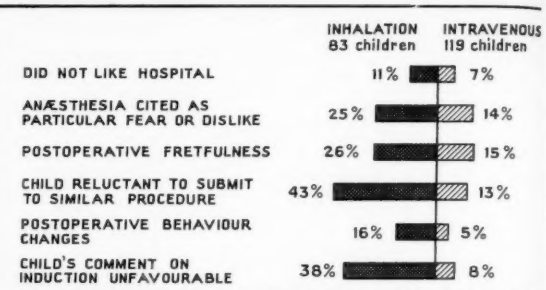

Fig. 5—Comparison between sequelæ of anæsthesia induced by inhalation and by intravenous injection.

Three patients (2%) in the whole series, therefore, could be regarded as showing psychic trauma due to anæsthesia. At first it seemed that the younger children were more susceptible to psychic trauma (table I). But in the final assessment, taking all factors into consideration, age had less statistical significance than had been expected. 18% of the children below 5¹/₂ years and 15% of those above this age fell into group 2 (table V).

Finally, in an attempt to assess the value of intravenous induction of anæsthesia, the results of analysis of the first questionnaire were compared with those from the previous study in which the children were anæsthetised by open induction (fig. 4*b*). The obvious and significant difference in the results (fig. 5) is heavily in favour of those children in whom anæsthesia was induced intravenously.

Conclusions

Of the hundred and forty-two children, most (84%) had not been in hospital before, but despite the anæsthetic and operation many (75%) were said to have enjoyed their stay. Still more (87%) would submit, in the opinion of their parents, without protest to a similar procedure if it became necessary.

The intravenous induction of anæsthesia in these children (without sedation) was technically successful in over 99% of cases, and only 3% were distressed during the induction period. In only 2% could the anæsthetic be incriminated as a cause of behaviour changes.

The results demonstrate clearly that psychic trauma is not an inherent part of anæsthesia and surgery, and that good results can be achieved without any drug premedication. This series may be useful as a baseline for assessing premedicants given to children.

In this series two factors seem to be mainly responsible for success—namely, the way the children were treated by everybody concerned and the method of inducing anæsthesia by giving thiopentone intravenously, which was neither frightening nor toxic.

In children admitted to hospital factors other than anæsthesia may be more often responsible for psychic trauma. Of the specific dislikes here encountered, 58% were not associated with the anæsthetic. Homesickness was not uncommon among both the successful and unsuccessful cases. Although it has always been accepted that the difficulties are greater in the very young, there was no significant correlation between age and success. But children under 3 years should not be admitted to hospital for elective surgery if this can safely be postponed.

Using this technique avoidance of psychic trauma depends not on the anæsthetist alone but on the whole

team. One person's lack of kindness and gentleness may utterly outweigh the highest degree of skill shown by any other.

I should like to record my appreciation of the assistance and tolerance shown by my colleagues—anæsthetists and surgeons alike. My thanks also go to the sisters and nurses, the theatre porters, and all concerned with the handling of these children; to the hundreds of parents who responded to the questionnaires; and to the thousands of children who directly and indirectly assisted me in this investigation.

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A PERSPEX ICTEROMETER FOR NEONATES

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THE icterometer is a simple device for estimating quickly the depth of jaundice in newborn babies at the cotside without taking a blood specimen. The principle is to blanch the baby's skin by pressure, and match the resulting shade of yellow against a colour scale.

The device is valuable as a means of (1) following the depth of jaundice in individual babies from day to day,

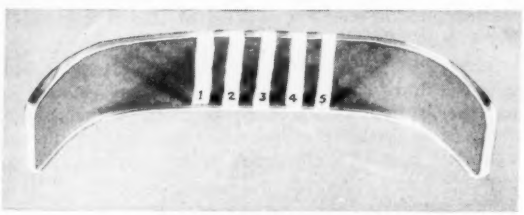

Fig. 1—The icterometer.

and (2) indicating which babies ought to have their serum-bilirubin estimated.

The icterometer (fig. 1) is a strip of transparent perspex, $^1/_8$ in. thick, $1^1/_4$ in. wide, and 7 in. long, curved at both ends for ease of handling. On its convex surface are painted five transverse yellow stripes, in slightly different shades.* These stripes and the spaces between them are $^3/_{16}$ in. wide. The stripes are numbered 1–5, the lightest in colour being 1, and the darkest 5.

Method of Use

When the icterometer is used, the painted (convex) side is pressed against the tip of the baby's nose until the skin becomes blanched (fig. 2). The yellow colour of the skin can then be matched with the yellow stripes on the scale. The reading is recorded according to the number of

* These were of ' Robbialac Colorizer ' paint no. 501, shades A, B, C, D, and E, made up in robbialac grey base undercoat.

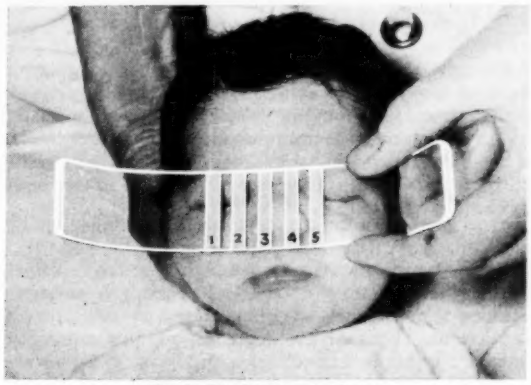

Fig. 2—The icterometer in use.

the best match; or, if the colour falls half way between two stripes, as $1^1/_2$, &c.

The nose is the obvious place for the test, because it is so easily accessible. I have tried using other parts of the body but have found that readings were quite different.

The instrument is washed with soap and water before being used on another baby. Disinfectants or boiling could damage the perspex or discolour the yellow paint.

The icterometer was originally devised in March, 1954, as a means of following the depth of jaundice in a baby from one day to the next. In this it has been highly successful, for it shows at once whether the baby's skin is more or less jaundiced than it was the day before. This is often all one wants to know. It also enables the depth and duration of the jaundice to be permanently recorded, which may be invaluable later on.

Correlation with Serum-bilirubin

In order to see how far the icterometer reading could be correlated with the serum-bilirubin level, a series of 229 comparative readings was made. The results (fig. 3) show broad agreement between the two methods, but the scatter is fairly wide, and one cannot deduce from a given icterometer reading what the serum-bilirubin level will be. This is not surprising, because the series comprises many different babies, and the icterometer is influenced

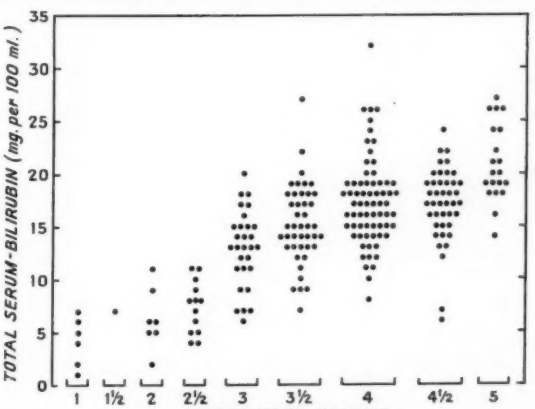

Fig. 3—Icterometer readings compared with total serum-bilirubin levels (estimated by Molloy and Evelyn's method). Each dot indicates one reading.

not only by jaundice but also by slight variations in skin colour between one baby and another.

Fortunately one is much more concerned in practice with the interpretation of serial readings in single babies than with random sampling of the kind shown in fig. 3; and my experience has been that when serial observations are made on individual babies from day to day, the serum-bilirubin levels and icterometer readings do in fact tend to rise and fall together.

A Screening Test

Recording the intensity of jaundice in premature babies during the first week of life is important because an exchange transfusion may be necessary to prevent kernicterus. Because the depth of jaundice cannot be judged by simple inspection, a great many babies are subjected to serum-bilirubin estimations to make sure of detecting the few at risk. By using the icterometer as a preliminary screening test, some of these serum-bilirubin estimations can be avoided.

At Northampton General Hospital we take 24 mg. per 100 ml. of total bilirubin (using the method of Molloy and Evelyn) as our threshold for replacement transfusion. It follows that an accurate laboratory estimation of the serum-bilirubin is needed as soon as a level of about 20 mg. per 100 ml. is exceeded. But fig. 3 shows that in comparative tests no serum-bilirubin levels over 20 mg. per 100 ml. were encountered in babies with icterometer readings of 3 or less. We have therefore made it our practice for the past $2^1/_2$ years not to ask for serum-bilirubin estimations until the icterometer reading is $3^1/_2$ or over; and we have no reason to believe that we have missed a case of kernicterus.

Disadvantages

The icterometer is so simple that there are obvious snags:

(1) The yellow stripes do not always give a perfect match with the baby's skin, but in practice this does not seem to matter, because different observers get closely comparable results.

(2) It may not be reliable in artificial light.

(3) It cannot be used for babies with bruised noses (e.g., following face presentation).

(4) Its use is limited in black-skinned or yellow-skinned babies, in whom it will merely show whether or not the jaundice is increasing from day to day. A Siamese baby, for example, had at birth an icterometer reading of 3, which rose gradually during the next few days to 5, and then fell back again to 3 and stayed there. This enabled us to spot her jaundice, and to say when it had passed its peak, but we had to invoke the laboratory to determine the extent of jaundice, because our scale was not calibrated for Siamese babies.

(5) Milia on a baby's nose are a nuisance, but do not prevent the use of the icterometer.

(6) When neonatal jaundice develops rapidly (as in blood-group incompatibility) the serum-bilirubin can rise so fast that the skin colour lags behind. Hence babies developing jaundice within 36 hours of birth should always have their serum-bilirubin estimated, for in these circumstances it would be dangerous to rely on the icterometer as a screening test.

(7) Cross-infection is an obvious possibility, but after more than 4 years the icterometer has not yet been incriminated. The risk could be reduced by having a separate icterometer for each baby.

(8) All the icterometers that I have used so far have been painted from five tins of robbialac paint made up in 1954. The colour shades of icterometers made from different batches of paint may not be identical with those I have described in this paper, although the makers of robbialac claim that their colorizer paints are standardised. The same general principles will apply, however, and the colour differences are unlikely to interfere with the usefulness of the icterometer as a rapid cotside test.

My thanks are due to the staff of the premature unit in the Barratt Maternity Home for testing and using the icterometer; to Dr. D. Phillpott and his laboratory technicians for their cooperation in calibrating it against the serum-bilirubin; to Mr. J. Pamely for fig. 1; and to Dr. W. J. A. Hall Turner for his help in collecting the data for fig. 3.

Icterometers are now manufactured (using the original tins of paint) by Thos. A. Ingram & Co., Ltd., Santon Works, Prescott Street, Birmingham, 18, at a cost of 9*s*. 6*d*. each for quantities of a dozen. For larger quantities the price will be lower.

CLINICAL ASSESSMENT OF DEPTH OF JAUNDICE IN NEWBORN INFANTS

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KERNICTERUS, the most important complication of neonatal jaundice, has three main causes:

(1) Rhesus incompatibility, where, because maternal blood-tests in pregnancy and the cord-blood findings at birth give reliable forewarnings, appropriate early exchange-transfusion can be undertaken.

(2) ABO incompatibility, where Tovey et al. (1959) found that the only important guides to treatment are the appearance of early jaundice and the frequent estimation of serum-bilirubin (to measure its approach to the potentially toxic level of 25 mg. per 100 ml.).

(3) Immaturity, the jaundice of which appears later but which requires the same control as that of ABO incompatibility (Crosse et al. 1958).

Odell (1959) has suggested that kernicterus may depend upon the diffusibility of bilirubin, and that this may be determined by its degree of coupling with plasma-albumin; he further postulates that this may explain the occasional case of kernicterus at low serum-bilirubin levels.

The relation of skin colour and serum-bilirubin has been the subject of discussion for many years.

Davidson et al. (1941) pressed a transparent tongue-depressor on the baby's skin and showed a qualitative relation between the degree of jaundice and the bilirubin level. Allen (1958) described the value of polished lucite in the early detection of jaundice, although Lathe et al. (1958) pointed out occasional high serum-bilirubin levels without apparent skin change. It is well known that as jaundice fades the skin colour lags behind the serum-bilirubin level.

A simple instrument, the icterometer, has been devised by Gosset (1960) to estimate the degree of skin icterus. We have used this in an attempt to determine whether skin colour bears any relation to serum-bilirubin levels. We set out to assess the value of this method as a screening test in neonatal jaundice, and, in view of the important observation of Davidson et al. (1941) that one baby had a serum-bilirubin level of 12·1 mg. without showing clinical jaundice, to assess the chances of missing a dangerously high level.

ICTEROMETER READINGS CORRESPONDING WITH INDIRECT SERUM-BILIRUBIN LEVELS

Icterometer reading	No. of observations	Serum-bilirubin (mg. per 100 ml., indirect)		
		Mean	S.D.	Range
2	4	5·55	1·61	3·9
2½	29	7·57	2·27	11·7
3	38	10·03	2·26	10·1
3½	66	12·31	2·50	12·3
4	27	15·73	3·03	11·7
4½	19	19·06	3·62	13·8

Method

Between December, 1958, and June, 1959, inclusive, there were 998 live births in the Birmingham Maternity Hospital. Of these, 669 babies who remained in hospital for six days or more were available for synchronous icterometer and bilirubin estimations. 165 babies were jaundiced, 59 being premature, and a total of 183 observations were made. Those babies with fading jaundice, and those who had recently had exchange transfusions were excluded. Towards the end of the study only those showing icterometer readings over 3 were included. Icterometer readings observed by one, two, or three of us never varied by more than a half reading. Blood was taken by venepuncture, or occasionally by heel prick, and bilirubin was estimated by the method of Lathe and Ruthven (1958). The differences between venous and heel-prick blood were not regarded as important in this correlation.

Results

The icterometer readings corresponding with the indirect bilirubin levels are shown in the table together with the mean, the standard deviation, and the range. The relation between icterometer readings and the mean indirect bilirubin level is shown in fig. 1.

From these data fig. 2 has been prepared to show the proportion of cases at or above a given bilirubin level that would be missed by taking a selected icterometer reading as a criterion.

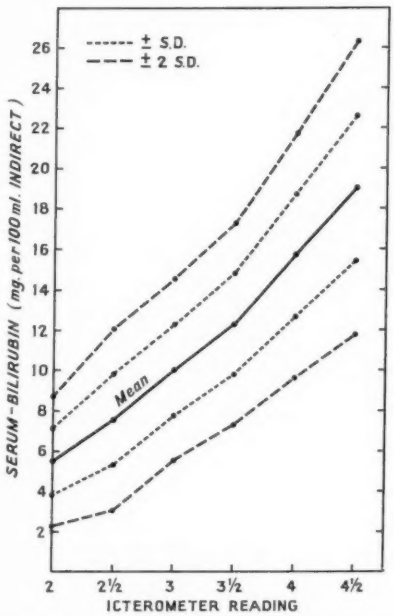

Fig. 1—Relation between icterometer readings and the mean indirect bilirubin level.

Curves are drawn for three adjacent icterometer readings within the critical region, and they are related to indirect bilirubin levels. Thus, for example, taking an icterometer reading of 3, only 1% of cases with an indirect level of 16 mg. per 100 ml. or more will be missed.

Discussion

This simple instrument, which can be carried in the pocket and washed after use as one washes one's hands, seems to have a place in the nursery for the newborn. Hitherto the timing of bilirubin estimations has depended on the unaided eye of the clinician, but this new instrument provides both a direct colour match and a means of expressing the blood, with the resultant pink colour, from the superficial skin layers. Odell (1959) points out that measurement of the serum-bilirubin itself by present methods gives no indication of the degree of saturation of the serum-proteins with bilirubin; possibly, as a measure of diffusible bilirubin and the risk of kernicterus, the degree of skin pigmentation may be as good or even better.

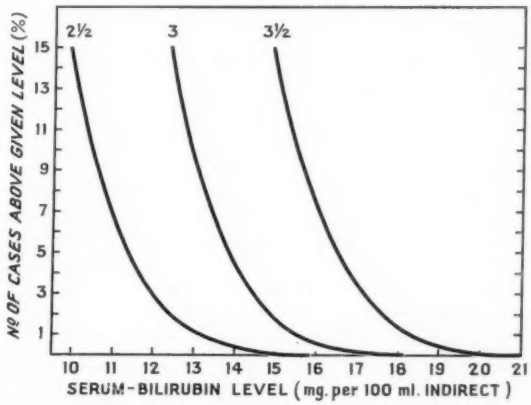

Fig. 2—Proportion of cases above a given bilirubin level that would be missed by using the icterometer.

For practical purposes our work suggests that, in cases other than those with rapidly increasing jaundice in the first twenty-four hours of life (such as in rhesus incompatibility), if the icterometer reading is 3 or below serum levels can be omitted, whereas above this reading blood studies should be undertaken. Our observations were made in daylight, but artificial daylight lamps seem to give comparable results at night, and would be useful in a neonatal department.

We are very grateful to Dr. Dorothy Barrow for help with the clinical side of this work; and to Mr. W. F. Johnson and Miss J. M. Reynolds for performing most of the bilirubin estimations. One of us (P. E. C.) was in receipt of a grant from the United Birmingham Hospitals endowment fund.

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ANTERIOR-CHAMBER IMPLANTS IN OPHTHALMIC SURGERY

NEW DEVELOPMENTS AND NEW USES

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THE posterior-chamber acrylic * lens was described by Harold Ridley (1951) and the anterior-chamber implant by Strampelli (1954). Since the Strampelli type of lens was introduced into this country in 1956 it has been used to treat many hundreds of patients, and it is now recognised as a useful aid where uniocular aphakia cannot be corrected by a contact lens (*Lancet* 1958).

Eye injuries are not uncommon in childhood and when they result in uniocular cataract or aphakia the problem is urgent. Amblyopia ex anopsia will probably complicate the picture within six to twelve months of the injury and is usually irreversible. Very few of these young patients can be fitted with contact lenses within this period and the anterior-chamber implant offers the only opportunity of restoring reasonable visual acuity and binocular function.

Some months ago I reported a series of 100 cases (Choyce 1959). In a second 100 I have used an implant differing in a number of respects from that originally designed by Strampelli. The two most important differences are:

1. Flattening of the anterior radius of curvature from 12 to 14 mm.
2. Reduction of the thickness of the haptic portion from 0·91 to 0·50 mm.

With this new thin implant the incidence of serious complications, such as endothelial corneal dystrophy, has been much lower. These wholly transparent implants can also be used to treat, with success, cases of uniocular high myopia in young persons; but the climate of opinion in this country is against their use to correct binocular myopia or hypermetropia, because this can be adequately corrected by spectacles or by contact lenses.

Obviously it would be an advantage if either the haptic or the optic portion of these implants could be made opaque, while the other portion remained clear. The problem is how to tint or colour the polymethyl methacrylate of which they are composed.

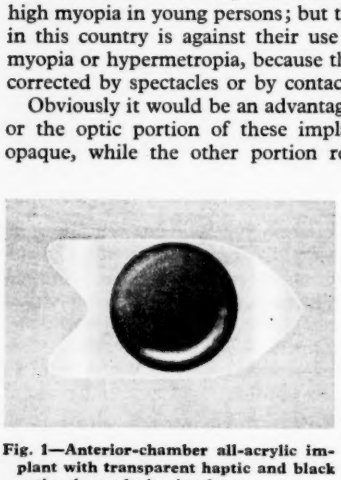

Fig. 1—Anterior-chamber all-acrylic implant with transparent haptic and black optic: the occlusive implant.

Black perspex is readily made by introducing carbon-black, and it can be thermally fused with transparent perspex so that one can make an implant with a clear haptic and a black optic, or vice versa. The result is a homogeneous piece of perspex (fig. 1) which has the same mechanical properties as an ordinary implant and therefore will not break into its black and transparent portions after introduction into the eye.

The implant with a black optic and a transparent haptic can be used to relieve intractable diplopia as in the following case:

A patient with a severe anxiety state was referred by the psychiatrist because of diplopia. Caused by a head injury in his teens, this remained constant and disabling despite numerous operations on the eye muscles. The conventional shade over the squinting eye afforded no relief.

Insertion of this occlusive implant relieved his diplopia and also his anxiety state. For the first time in many years he is usefully employed and leading a contented home life. If later he should need to make use of the sight in this eye, the implant can be removed.

This type of implant can also be used to improve the appearance of a blind eye with an ugly complicated cataract such as is often seen after longstanding retinal detachment.

The reverse of this type of implant—i.e., with black haptic portion and a clear central optic—could be used in many cases where the iris is absent or deficient; but the large black pupil which would result would be very unsightly. Imperial Chemical Industries were therefore asked to find some way of colouring the polymethyl methacrylate with pigments which would not diffuse into the eye and irritate it. They have produced a partial answer in the form of perspex in three shades of blue and one shade of dark brown which (like black perspex) can be thermally fused with a clear central optic. At the moment, matching a green iris is rather unsatisfactory. Experience shows that, when inserted into the anterior chamber of a patient with a green or tawny iris, a brown haptic portion looks better than any of the blues.

Fig. 2—Anterior-chamber implant with coloured haptic and transparent optic: for cases with iris deficiency.

Thus the surgeon can introduce into the anterior chamber an implant which appears to fill in a coloboma of the iris with a haptic portion of appropriate hue. If the coloboma is large, the diameter of the optic can be reduced to 2, 3, or 4 mm., thus sharpening the retinal image, as by the use of a stenopæic aperture (fig. 2). If spherical ametropia is also present, a suitable correction can be moulded on the posterior surface of the central optical portion. The following are examples of cases treated in this way:

1. A youth of 16, with partial albinism, was also a low-grade myope. Insertion of an implant, with brown haptic and a 4 mm. optic with suitable myopic correction, has almost eliminated the photophobia from which he has always suffered. The nystagmus is greatly reduced and the visual acuity, which was 6/60 with a myopic correction, is now 6/18.

2. An engineer with a heavily pigmented brown iris sustained a perforating corneal wound with an iris prolapse, which resulted in a substantial temporal coloboma of the iris. He suffered intense photophobia, not relieved by a tinted contact lens. He had to wear a shade over this eye most of the time. Insertion of an implant with a brown haptic has relieved the photophobia, and from a distance of a few feet the eye appears normal.

3. A blue-eyed patient sustained a perforating wound in childhood which left him with a large iris coloboma above and temporally, and aphakia. Before operation his corrected visual acuity was 6/60. After insertion of an implant with a dark-blue haptic and with an optical portion which corrected the aphakia, the photophobia has been eliminated and the visual acuity is 6/18.

* Acrylic = polymethyl methacrylate or 'Perspex'.

Congenital aniridia seems to offer another promising field for the use of this type of implant.

I am indebted to Mr. P. M. Caudell of the instrument department of Rayner Ltd., and to the plastics division of Imperial Chemical Industries, for their collaboration in the development of these new implants.

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REDUCTION OF SPUTUM VISCOSITY BY A WATER AEROSOL IN CHRONIC BRONCHITIS

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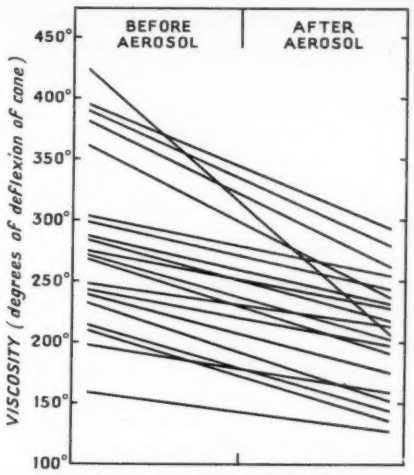
SPUTUM in chronic bronchitis is of two main kinds: "mucoid", which is clear, gelatinous, and viscid; and "purulent", which is yellow, opaque, and less viscid. Although purulence of sputum is shortlived when suitable antibiotics are used, mucoid sputum is not reduced by chemotherapy (May 1953), and persistent viscid mucoid sputum is an important manifestation of chronic bronchitis (Oswald 1954). Mucoid sputum is a mucoprotein gel, its viscosity depending on its mucoprotein content and the degree of hydration of the gel. To reduce the viscosity of mucoid sputum, aerosol inhalation of enzymes and detergent solutions has been used (*British Medical Journal* 1954). Good results have been reported with solutions of trypsin (Unger and Unger 1953, Harwood Stevenson and Kinnier Wilson 1957), but others have thought it too irritant and have not been impressed by its mucolytic action in vivo (Farber et al. 1954, Forbes and Wise 1957). Recently a less irritant derivative of trypsin—chymotrypsin—has been used by insufflation of the dry powder into the bronchial tree, with promising results (Robinson et al. 1958).

The aerosol detergent used most often has been 'Alevaire' (which is a solution of a detergent with sodium bicarbonate and glycerin), and symptomatic benefit has followed its use; but a control solution containing water and sodium bicarbonate without detergent has been shown to facilitate expectoration as effectively as alevaire. Moreover, an hour's aerosol inhalation with either alevaire, the control solution, normal saline solution, or water is followed by a reduction in sputum viscosity of approximately equal degree (Palmer 1957). This suggests that these solutions owe their effect to their water content. I have, therefore, measured the effect of the aerosol inhalation of water on the viscosity of mucoid sputum in chronic bronchitics.

Method

Twenty inpatient chronic bronchitics were admitted to the trial. Measurements were made in the afternoon because, in a period of control observation, the viscosity of the sputum was found to be most constant at this time.

Each patient was studied for three hours. In the first hour sputum was collected in a dry container and its viscosity measured (vide infra). In the second hour about 15 ml. of water was nebulised in a 'Collinson' or 'Oxygenaire' apparatus by oxygen. In this way the water is administered as a fine "dry" mist with a particle size of 0·5–3·0μ. Sputum produced for one hour after the inhalation was collected and its viscosity measured. Patients were asked whether expectoration was easier after the inhalation, and improvement in rhonchi was noted.



Effect of water aerosol on viscosity of sputum.

Viscosity was measured in a cone and plate viscometer which was specially designed for this purpose (Palmer 1957). Viscosity is expressed in degrees of rotation of the cone—the deflection increasing with greater viscosity.

Results

The results (see figure) show that there was a reduction in sputum viscosity in all twenty patients after the aerosol inhalation of the water mist for one hour, and that generally this was greatest where the initial viscosity was highest. The mean reduction in viscosity was 71·4° (21·5%) (range 221–23°). All the patients felt that coughing was easier afterwards, and notable reduction in rhonchi was observed in many.

Comment

An hour's aerosol inhalation of water reduced viscosity and greatly assisted expectoration in chronic bronchitics with viscid mucoid sputum. Reduction in viscosity was greatest in those with the most viscid sputum, probably because the mucoprotein gel takes up water most avidly in this type of secretion.

This treatment is non-irritant, is devoid of toxic effects, and is physiological in action. In this trial oxygen was used to aerolyse the water. In patients with chronic bronchitis and emphysema and incipient respiratory failure (carbon-dioxide narcosis) continuous oxygen for an hour may be contraindicated (Westlake et al. 1955). For these patients the water may be aerolysed by compressed air, or compressed air alternated with oxygen.

Summary

In twenty chronic bronchitics with mucoid sputum, aerosol inhalation of a water mist for an hour reduced sputum viscosity and made expectoration easier.

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AUTOIMMUNE HÆMOLYTIC ANÆMIA TREATED WITH VENOM ANTISERUM

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VENOM antiserum (' Antivenene ') is concentrated polyvalent anti-snake-venom serum, prepared at Haffkine Institute, Bombay, against the venoms of the four common poisonous snakes of India—i.e., cobra, common krait, Russell's viper, and saw-scaled viper. When injected intravenously with the venom into white mice each millilitre of the serum neutralises not less than the following quantities of dried venom: cobra 0·6 mg.; common krait 0·45 mg.; Russell's viper 0·6 mg.; and saw-scaled viper 0·45 mg. If venom antiserum is given intravenously or intramuscularly the antibody in autoimmune hæmolytic anæmia is quickly removed, the antiglobulin test becomes negative, and hæmolysis ceases speedily.

Material and Methods

Venom antiserum was given to twenty-seven patients, comprising twenty-two men and five women. Their ages ranged from 19 to 32 years, and the duration of anæmia was from 3 weeks to 2 years. Twelve gave a past history of malaria 3–7 years previously, and seven had evidence of ankylostome infection, but antimalarial therapy and disinfestation before treatment with venom antiserum had not altered the course of the disease. Two women were in mid-pregnancy. Twenty-one patients were seen between the cold months of October and March. Four cases were acute, and the other twenty-three were chronic.

A clinical as well as a serological remission, as in case 26 (vide infra), was desired. Venom antiserum was effective by both the intravenous and the intramuscular route, but the intravenous route was used for treating severe cases only. It usually sufficed to inject 20 ml. of concentrated venom antiserum intravenously and 20 ml. intragluteally, the intramuscular injection being repeated on the 3rd, 7th, and 14th days of treatment. In very severe cases an additional intravenous injection was required on the 3rd day for complete clinical and serological remission. In mild cases 20 ml. of concentrated venom antiserum injected intragluteally on the 1st and 14th days was usually enough. But sometimes complete serological remission was not obtained with this dose, as in case 11 (vide infra), and we now think an additional dose of 20 ml. on the 3rd day is advisable.

Results

The mild cases showed no further hæmolysis after the first injection of venom antiserum, and the blood-picture improved steadily.

The severe cases showed a dramatic remission in constitutional symptoms within 48 hours of the first intravenous and intramuscular injections of venom antiserum, and the patient was well on the way to recovery within a week.

During follow-up for 5–26 months there were no clinical failures.

Mode of Action

Venom antiserum was first used in the treatment of autoimmune hæmolytic anæmia because it prevented hæmolysis in blackwater fever (Singh and Singh 1944). Although it has always been effective in autoimmune hæmolytic anæmia so far, the mechanism by which it prevents hæmolysis is not yet absolutely clear. The serological results in the following cases indicate that venom antiserum rapidly " removes " the antibody and potentiates in vivo an unknown protective mechanism.

Case 26 (blood-group B) had a powerful, apparently non-specific, agglutinin acting at the following titres:

	37°C	4°C
Own cells	512	8192
Other cells	64	2048

The direct Coombs' test was positive. No separable components for O, A_1, or B cells were present; the specificity of the autoagglutinin was unknown.

5 days later, after a course of amodiaquine (' Camoquin '), which had been administered for suspected malaria, the antibody concentration was not significantly different, and the direct Coombs' test was still positive. But 2 days after venom antiserum was given the antibody titre dropped appreciably:

	37°C	4°C
Own cells	0	64
Other cells	0	16

and the direct Coombs' test was negative.

Inhibition tests were made in vitro using the original sample of the patient's serum. An ampoule of dried venom antiserum was reconstituted with 10 ml. distilled water. This solution was diluted 150 times to attain a concentration corresponding roughly to the serum level immediately after the intravenous injection of venom antiserum, and to inactivate agglutinins for human erythrocytes in the reconstituted venom antiserum. Equal volumes of diluted venom antiserum and the patient's serum were mixed, left at room temperature for 30 minutes, and then tested against various erythrocytes; there was no inhibition of agglutination.

Thus the therapeutic response to venom antiserum cannot be attributed to the direct inhibition of the autoagglutinin.

Case 11.—The antibodies in the serum of this patient have already been described (Bird 1951). After a 2-week course of venom antiserum, given as for a mild case, her autoantibodies became active only at low temperatures. 6 months later they were active against her own cells at 37°C, but she showed no signs of overt or masked hæmolytic anæmia, and the direct Coombs' test was negative. Some in-vivo protective mechanism, therefore, seemed to be at work.

We are grateful to Lieut.-General B. Chaudhuri, Director-General, Armed Forces Medical Services, India, for permission to publish this report.

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"... if someone were to plead the virtues of an intellectually pastoral existence, not merely quiet but acquiescent, and with no more than a pensive regret for not understanding what could have been understood; then I believe I could listen to his arguments and, if they were good ones, might even be convinced. But if he were to say that this course of action or inaction was the life that was authorised by Nature; that this was the life Nature provided for and intended us to lead; then I should tell him that he had no proper conception of Nature. People who brandish naturalistic principles at us are usually up to mischief. Think only of what we have suffered from a belief in the existence and overriding authority of a fighting instinct; from the doctrines of racial superiority and the metaphysics of blood and soil; from the belief that warfare between men or classes of men or nations represents a fulfilment of historical laws. These are all excuses of one kind or another, and pretty thin excuses. The inference we can draw from an analytical study of the differences between ourselves and other animals is surely this; that the bells which toll for mankind are—most of them, anyway—like the bells on alpine cattle; they are attached to our own necks, and it must be our fault if they do not make a cheerful and harmonious sound."—Prof. P. B. MEDAWAR, *Listener*, Dec. 24, 1959, p. 1118.

Preliminary Communications

CORTICOSTEROID PURPURA

WE have found that senile purpura—which is normally confined to the extensor surface of the arms, the back of the hands, and the sides of the neck and face—is accounted for by two abnormalities. Senile degeneration of collagen in susceptible areas accounts for the characteristic shape and size of the lesions, whilst the absence of any inflammatory cellular reaction is responsible for slow resorption of the blood and for absence of the colour changes that normally accompany bruising in younger people.

In many respects the lesions sometimes seen in patients who have been having adrenal corticosteroids are similar to senile purpura. In eleven such patients extensive hæmatological studies [1] did not show any cause for the purpuric lesions. Breakdown of collagen [2] and impairment of inflammatory cell reactions are well-known effects of giving hydrocortisone and its analogues. We therefore suggest that the lesions of corticosteroid purpura may be explained in a similar way to those of senile purpura.

INVESTIGATION

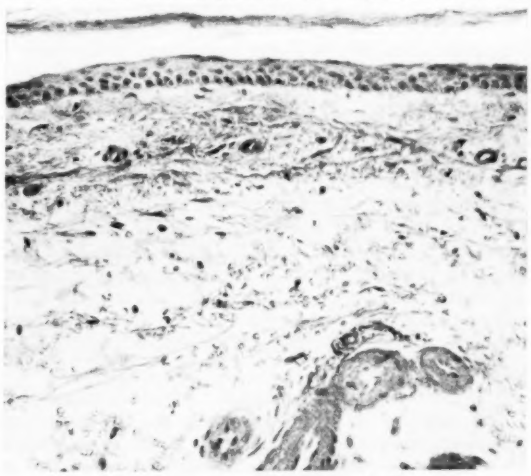
Venous blood was drawn into a tuberculin syringe without anticoagulant, and 0·1 ml. was injected back immediately into skin on the backs and fronts of the forearms and lower legs. Biopsies were done a week after injection of blood. Spontaneous lesions of " corticosteroid purpura " which had been present for about a week were biopsied for comparison.

It is difficult to define corticosteroid purpura precisely. Our patients were all elderly; but their lesions, though they resembled those of senile purpura, had appeared only after long-continued treatment with corticoids. More importantly, some of them were in areas not normally affected by senile purpura—namely, the legs below the knees and the fronts of the forearms. No patient had any other reason for purpura; the platelet-counts were all normal, and the tourniquet tests negative.

Details of the five patients who fulfilled these criteria are given in the table.

The lesions on the extensor surfaces of the arms resembled senile purpura in shape and size although they tended to be more circular and occasionally linear. The extensor surface of the arm and the dorsum of the hand was always the worst affected. The patients all related the purpura to trauma, which was usually trivial. The lesions of senile purpura are likewise precipitated by trauma, although the patients are often unaware of this.

Abnormal spread of injected blood was observed in all patients, and the induced lesions resembled spontaneous corticosteroid purpura both in immediate appearance and in the slow rate of resorption. Brownish discoloration was seen in association with some of the lesions of corticosteroid purpura (spontaneous and induced) but most lesions remained unchanged for weeks, as in senile purpura. Sections of induced and spontaneous lesions showed the same features in all patients (see figure). Gross disorganisation of the dermal collagen was evident in stained preparations (van Gieson). Phagocytosis of erythrocytes by tissue histiocytes, such as has been reported after injection of blood into normal skin of animals [3] and man,[4] was never seen.



Induced corticosteroid purpura (×225).

Blood was injected intradermally into the front of the leg a week before the biopsy. This section shows sparse collagen which is abnormally distributed; the phagocytosis that follows the extravasation or injection of blood into the skin is absent.

CONCLUSIONS

Tattersall and Seville [5] suggested that in elderly people atrophy of collagen leads to easy rupture of the minute vessels of the skin. In patients with corticosteroid purpura

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FIVE WOMEN WITH CORTICOSTEROID PURPURA

Disease	Age	Steroid		Site of purpura				Response to injected blood			
		Type	Duration (months)	Forearm		Lower leg		Forearm		Lower leg	
				Back	Front	Back	Front	Back	Front	Back	Front
Hypoplastic anæmia ..	69	Prednisolone (5 mg. t.d.s.)	11	+	+	−	−	A	N	N	N
Rheumatoid arthritis ..	54	Triamcinolone (4 mg. b.d.)	18	+	−	−	+	A	N	N	A
Rheumatoid arthritis ..	71	Prednisolone (5 mg. b.d.)	12	+	+	−	−	A	N	N	N
Rheumatoid arthritis ..	58	Methylprednisolone (4 mg. t.d.s.)	18	+	+	+	+	A	N	A	A
Rheumatoid arthritis ..	65	Prednisolone (5 mg. t.d.s.)	30	+	−	−	+	A	N	N	A

All details refer to the time of investigation. The normal response (N) to injected blood was a bleb. The abnormal response (A) was no bleb with increased spread.

the histological appearance indicates a similar explanation. In both senile purpura and corticosteroid purpura the abnormal structure of the skin collagen is probably the reason for the abnormal spread of extravasated or injected blood and for the failure to raise a bleb.[6] In the aged the absence of a normal cellular response delays resorption of extravasated or injected blood, and purpuric lesions thus persist. The same thing happens, presumably, if the inflammatory cellular response is inhibited by the corticosteroid.

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PULMONARY DIFFUSING CAPACITY
AN IMPROVED SINGLE-BREATH METHOD

IN the single-breath method of measuring pulmonary diffusing capacity for carbon monoxide (D_L), introduced by Forster et al.,[7] the estimates of D_L were found to vary with the time of breath-holding and the portion of the expirate sampled. Although the observations were made on normal subjects, they were interpreted by these authors as evidence of regional inequality of both ventilation and gas transfer.

In a theoretical investigation of the basis of the single-breath method[8] we have shown that the explanation of the anomalous variations in D_L lies in the experimental complexities of the method rather than the physiological complexity of the normal lung. The rate of absorption of carbon monoxide during inspiration and expiration differs appreciably from the rate during breath-holding assumed by the simple equation used in the calculation of D_L. Furthermore, the Forster method, in ignoring the time taken to collect the sample of alveolar gas, critically exaggerates the effects of the alveolar-volume changes inescapably associated with the single-breath method.

These apparent variations in D_L may be virtually eliminated by the following procedures:

(1) Start collecting the sample at the earliest possible moment compatible with an adequate washout of the physiological dead space.

(2) Collect as small a sample as practicable, e.g., less than 1 litre.

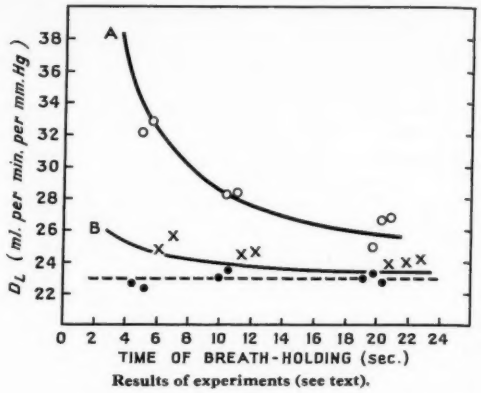
(3) Allow for the time taken to collect the sample by measuring breath-holding time from the beginning of inspiration to the mid-point, in time, of sample collection.

(4) Allow for the effect of inspiration by subtracting $^3/_{10}$ of the inspiratory time from the above to give a final "effective" breath-holding time.

Procedures 1 and 2 minimise the effect of changes in alveolar volume during expiration. Early sampling is more important than size of sample. Procedure 3 minimises error inherent in a larger sample.

The figure illustrates the results of seven experiments on a healthy young man.

The open circles represent experiments in which approximately 2·6 litres of expirate was collected after the rejection of the first litre (for washing out the physiological dead space), the D_Ls being calculated by Forster's method. The crosses are the same experiments, the D_Ls being calculated using the suggested "effective" breath-holding time. The closed circles are the results of a method, described below, in which 85 ml. samples were taken after the expiration of 1 litre. It will be seen that this method gives a virtually constant D_L of 23 ml. (S.T.P.D.) per min. per mm. Hg, shown by the horizontal dotted line.



Results of experiments (see text).

From our mathematical analysis[8] it is possible to predict the changes in D_L with breath-holding time arising from the use of Forster's method of calculation. The curved line A shows the predicted changes for this subject, assuming that his real D_L is constant and equal to 23 ml. (S.T.P.D.) per min. per mm. Hg. Similarly, the line B shows the expected improvement when using the suggested "effective" breath-holding time. From the good agreement between the predicted changes, A and B and their corresponding observed values, we conclude that this subject has a constant D_L of 23 ml. and that the apparent variation using Forster's method of calculation is an experimental artefact.

AN ALTERNATIVE (SMALL-SAMPLE) METHOD

It is theoretically desirable to take the smallest practicable sample at the earliest possible moment in expiration compatible with an adequate dead-space washout. We approached these conditions by collecting an 85 ml. sample in an evacuated tonometer, one end of which was inserted into the expirate airway near the mouthpiece. With this arrangement, the collecting period is very short (less than 0·2 sec.) and sampling can be carried out either by turning a tap on the tonometer, or with an electromagnetic valve triggered by movement of the spirometer after any desired volume has been expired.

The sample is too small to be passed through gas analysers in the ordinary way. Either it must be diluted with an appropriate volume of air or, more conveniently, the sampling tube may be connected in closed-circuit series with the analysers and a roller pump and the contents of the system circulated until a steady reading is obtained. No allowance need be made for the dilution, for we are concerned only with the ratio of carbon monoxide to helium concentration in inspirate and expirate samples.

The advantages of the method are:

1. The small sample volume and negligible sampling-time satisfy the theoretical requirements for the best estimate of diffusing capacity.

2. Samples can readily be obtained from subjects of small vital capacity.

3. Samples can be stored for later analysis so that a group of subjects can be examined without interruption.

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7. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., Morton, J. W. *J. clin. Invest.* 1957, **36**, 1.
8. Jones, R. S., Meade, F. (to be published).

SUMMARY AND CONCLUSIONS

Improved procedures for the single-breath method of estimating pulmonary diffusing capacity are described.

These eliminate the anomalous variations of D_L with breath-holding time, observed using Forster's method. These arise from neglect of the effects of alveolar-volume changes during the experiment and from the use of an inappropriate breath-holding time.

At 10 seconds breath-holding time the alternative methods give a D_L which is about 20% lower than that given by Forster's method with a normal subject.

In any of its forms, the single-breath method of estimating pulmonary diffusing capacity is theoretically justified only in respect of ideally normal subjects. As this qualification applies equally to the suggested improvements, there still remains the problem of interpreting such data in the presence of inequality of ventilation, perfusion, and membrane property.

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Reviews of Books

Outline of Human Genetics

L. S. PENROSE, M.A., M.D., F.R.S., Galton professor of eugenics, University College London. London: Heinemann. 1959. Pp. 146. 12*s*. 6*d*.

THIS book is an outstandingly successful attempt to cover the whole field of human genetics in little more than a hundred pages. After a historical introduction, the reader is taken through single-gene effects, population genetics, linkage of genes, the interaction of environment and heredity, eugenics and dysgenics. These sections are models of writing, simply phrased, but exact. The admirable balance shown, for example, in the section on the mutagenic effects of radiation is, one would like to think, one of the products of a medical education as well as a lifetime of study of human genetics.

The most difficult chapter is perhaps the last—on eugenics. This is a subject which involves social and ethical considerations as well as scientific, and while Professor Penrose discusses negative eugenics with good sense and humanity, his concept of positive eugenics may be thought unimaginative and perhaps unduly pessimistic. On all the more scientific issues, however, he is clear and wise.

Principles of General Physiology

5th ed. Vol. 1: *The Physico-chemical Background*. L. E. BAYLISS, PH.D., department of physiology, University College, London. London: Longmans, Green & Co. 1959. Pp. 520. 55*s*.

General Principles of Physiology by Sir William Bayliss has been a delight and stand-by for biologists for many years, and even now, when some of its views need modification in the light of more recent knowledge, the book can stimulate, inform, and give pleasure. This new edition by Sir William's son has been eagerly awaited and it will not disappoint. Perhaps it should not be called a new edition, since Dr. Bayliss has rewritten nearly the whole of the original and has found it necessary to produce the new book in two volumes, which certainly makes for easier handling. He has been driven to divide the book by the great increase in knowledge and importance of that borderland between biology, physics, and biochemistry, so that before general physiology can be profitably discussed it is necessary to give some account of the basis of many of our beliefs. So far, only the first volume dealing with the physicochemical background of physiology has appeared, and it will prove an invaluable book of reference.

The information gathered together here is mostly scattered in journals or textbooks not usually known to biologists. If the reader wishes to delve further he can use the references at the end of each chapter. The book is not bedtime reading except for those who already know the answers. It is solid worth and needs much digestion, but it provides information which all students of biology should know, and it is written so that the main points can be grasped by all, even if the finer points are missed. It covers the following subjects: energy, chemical reaction, solutions, electrolytes, surface phenomena, the colloidal state, catalysis, oxidation and reduction, light and other radiations, and passages of substances through membranes. This list at once shows what immense changes have taken place in knowledge and mode of thought since the original book was written. The new book intelligibly presents these important bases of biology in less than 500 pages—a feat of selection and compression.

In a preface the author points out that times have changed and that many of the unusual features, "the frills", of the original have had regretfully to be omitted. Many readers will regret it too, and feel that this functional and streamlined age loses much when scientific writings must be purely factual, concealing as far as possible the personality of the writer. But no convention can completely hide the character of the writer, and one is aware that this book is the outcome of a balanced and intelligent mind with something of Sir William's philosophical attitude.

Synopsis of Ophthalmology

WILLIAM H. HAVENER, M.D., M.S., professor of ophthalmology, Ohio State University. St. Louis: C. V. Mosby. London: Henry Kimpton. 1959. Pp. 288. 50*s*.

THIS compact handbook is addressed primarily to the physician, and its seventeen chapters outline concisely and lucidly the main features of the ocular problems likely to confront him. The presentation is severely practical, and the emphasis upon essential diagnostic features and early treatment before specialist advice is available is admirable. There is an excellent chapter on the examination of the eye, and the diagnosis and management of the "red eye" and ocular injuries are then considered. Strabismus, uveitis, glaucoma, degenerative diseases, and developmental anomalies are considered separately, and a useful section on the symptomatology of eye disorders is also included. The chapters on medical ophthalmology and neuro-ophthalmology are necessarily very condensed; but they are nevertheless valuable for the sound way in which many of the ocular signs and implications of general and intracranial disease are presented. The many illustrations are well chosen; but their value would be much greater if more of them could be in colour.

I Am an Alcoholic

RAYMOND BLACKBURN. London: Allan Wingate. 1959. Pp. 218. 15*s*.

THE title is misleading, for the greater part of this readable book is a relatively teetotal autobiography of Mr. Blackburn's interesting years in the Army and politics. He traces his political movement from hereditary conservatism via reactive socialism to disillusionment with the main parties and an independent position: he was one of the young post-war politicians who, had they not quitted the House, might have made a lot of difference to the contemporary political scene. Enjoying as he did a close friendship with Sir Winston Churchill, he is able to give many intriguing sidelights upon the momentous events and personalities that followed the war. His subjective but intelligent account of the slide into London's "Skid Row" makes quite good reading, though it adds little to what is already all too well known. Too much has perhaps been written about prisons "from the inside", but Mr. Blackburn's legislative reflexes lead him to make a few sound suggestions based on his experiences in two—notably, an intensive land-reclamation programme using prison labour. But sadly as his life has turned out, Mr. Blackburn's inclination to be cynical will not win many readers' sympathy; and

others will be discouraged by some wrongly spelt names. Some of the most relevant events are omitted, and it is never really clear what made this young man tick, or what were the dynamics of his downfall.

Basic Physics in Radiology

L. A. W. KEMP, B.SC., PH.D., F.INST.P., chief physicist, The London Hospital. R. OLIVER, M.SC., F.INST.P., A.M.I.E.E., principal physicist, department of radiotherapy, United Oxford Hospitals. Oxford: Blackwell Scientific Publications. 1959. Pp. 329. 35*s*.

THIS book covers, for the first time in one volume, the basic elements of statics, dynamics, magnetism, and electricity required for the diploma and membership examinations for students of radiology and radiography. The text is clear, concise, and adequately illustrated. Only the essential mathematical proofs are included, and many of these are set out in a separate chapter. Interest is maintained by many practical problems related to radiology, and by selected questions from previous examination papers. This book is a worthy companion to *A Student's Radiological Mathematics*, and may well become the standard textbook of physics for students of radiology and radiography.

Peaceful Uses of Atomic Energy (Vol. 26: *Isotopes in Medicine*. Geneva and New York: United Nations Organisation. 1959. Pp. 464. 92*s*.). This collection of papers presented at the United Nations conference in Geneva in 1958 is a useful permanent record of what was said. Though it contains little that is new to workers in the special fields discussed, it is a monument to a remarkable organisation that collected the data and published it so quickly; and it is beautifully and very accurately produced. To most doctors its chief interest may lie in the way it illustrates the ubiquity of interest in isotopes, and the technical achievement it demonstrates in what some people would call backward countries.

New Inventions

PLASTER TURNING FRAME

IN many conditions a plaster bed is the ideal means of immobilisation. But plaster beds have always had two disadvantages. If the plaster is mounted on a heavy wooden frame the patient cannot be turned without sacrificing immobilisation. On the other hand, if plaster turning cases are used, turning or "nursing" the patient is a major operation which takes a long time and leaves a trail of nurses with sprained wrists and strained backs.

The apparatus illustrated has been produced in the splint-shops of the Royal Sea Bathing Hospital from which it may be had at cost price.

A pair of split wheels rotate in a cradle (fig. 1). Anterior and posterior plaster cases—which should, when in place, be separated by $1^1/_2$ to 2 in.—are easily attached by shaping a wooden block at each end and inserting wood-screws.

When the patient is to be turned, two nurses, having only about a 6-lb. lift with each hand, simply place the other half of the plaster over the patient, approaching from the foot of the bed (fig. 2). The wheels are self-centring, and the actual turning can be done with one hand (fig. 3). The whole procedure can be completed in 30 seconds.

If frequent turning is necessary, the half-plaster not in use can be suspended over the patient from a double Balkan beam by four weights and pulleys. The nurses have only to pull the plaster down and release four dog-lead clips, and then after turning reattach the clips to the other half. Leather "dice-throwers" are provided to cover the wheel "corners" between turnings.

The frame can, of course, be used indefinitely and is indestructible. No oil is needed.

This apparatus was first demonstrated at the annual meeting of the British Orthopædic Association, at Oxford, in October, 1958.

Royal Sea Bathing Hospital, Margate, Kent F. G. ST. CLAIR STRANGE F.R.C.S.

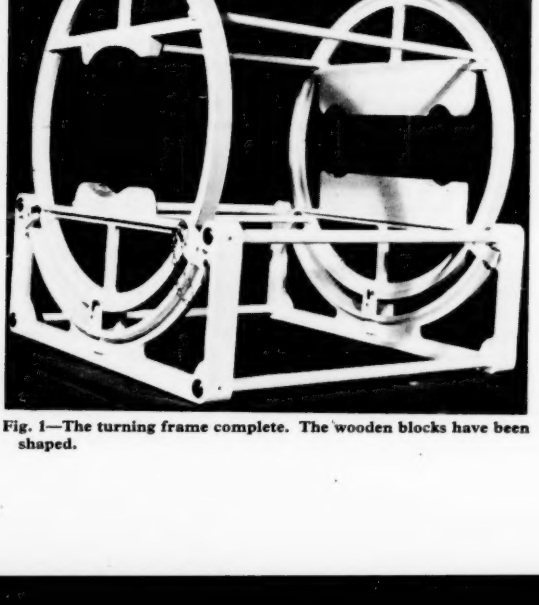

Fig. 1—The turning frame complete. The wooden blocks have been shaped.

Fig. 2—Patient on posterior plaster bed, with nurses placing the anterior plaster in position.

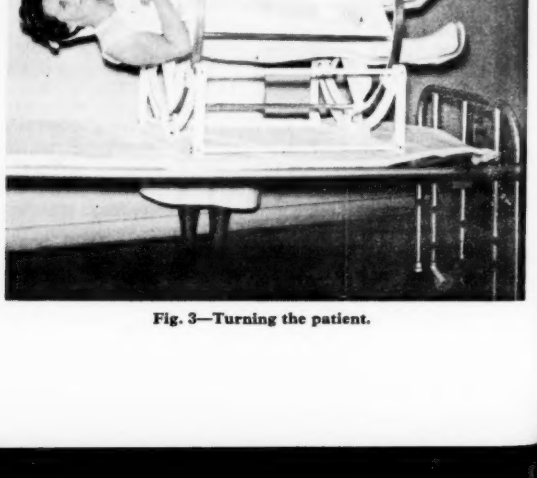

Fig. 3—Turning the patient.

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Poliomyelitis Vaccines

KILLED poliomyelitis vaccine can prevent paralytic poliomyelitis: this was demonstrated in a statistically sound controlled trial in the U.S.A.,[1] and subsequently confirmed in this country by a similar trial.[2] These trials showed that a primary course of vaccine was about 70% effective in preventing paralytic poliomyelitis (this means that the attack-rate in the vaccinated was 30% of that in the unvaccinated). There were, therefore, high hopes that poliomyelitis would dwindle into clinical and epidemiological insignificance, although many authorities still believed that the final answer might be an attenuated vaccine—mainly because of doubts about the duration of immunity conferred by killed vaccine. A living vaccine is thought likely to give a durable immunity because of the finding of PAUL et al.[3] that poliovirus antibodies apparently persisted for forty years in an isolated Eskimo population; and a living vaccine has been favoured because yellow fever and smallpox are successfully controlled in this way (though the immunity after smallpox vaccination is not lifelong). On the other hand, poliovirus neutralising antibodies fall in titre during convalescence at very much the same rate as they decay in people vaccinated with killed or attenuated virus;[4–6] so the superiority of living vaccine in this respect cannot be taken for granted.

Unfortunately, despite the widespread use of killed vaccine, there have been several substantial outbreaks of poliomyelitis, especially in the U.S.A.: in 1959 there were almost certainly as many paralytic cases in the U.S.A. as there were in 1956. This situation has led to disquiet lest the vaccine should be proving less effective than was to be expected from the Francis report,[1] and it has also stimulated intense interest in attenuated-virus vaccines. Soon after the Francis report appeared, the Cutter disaster led to changes in manufacturing and safety-testing requirements for killed vaccine. It is clear that these changes produced a safe product—but was potency sacrificed? There is some evidence that the antigenic potency of American vaccines has declined: for example, SALK [7] has found, in a survey of children in Pittsburgh, that the antibody response in 1956 was much superior to that in 1958. Similarly, other workers in the U.S.A. have reported very low levels of antibody response in children. In BARR's experience [8] more than 50% lacked antibodies to type-1 and type-3 virus after three doses. Fox et al. [9] recorded similar experiences and also found that Salk vaccination did not appear to prevent natural infection of the alimentary canal with polioviruses, whereas naturally acquired antibodies did prevent infection. This difference is probably due to differences in circulating antibody titre, but it has been suggested that a local alimentary immunity conferred by natural and attenuated virus infection is responsible.[10] The vaccine used in the Medical Research Council trials in this country, which assessed both antigenic potency and effectiveness in preventing paralysis, was made with material that had passed the more stringent control tests introduced in this country after the events in America. The impression that killed vaccine may be less effective than had been expected was to some extent supported by preliminary data published by the U.S. Communicable Diseases Center in poliomyelitis surveillance reports, which showed substantial numbers of cases in individuals given three doses of vaccine. Recently, however, a new report [11] gives reassuring preliminary figures of vaccine effectiveness. From census figures and an extensive sample survey of immunisation status, age-specific attack-rates for unvaccinated and vaccinated individuals were calculated. From these figures the effectiveness of the vaccine can be estimated. In 1958 and the first 45 weeks of 1959 for age-groups up to 14 the estimates exceed 90% against paralytic poliomyelitis for those given three or more doses of vaccine. It must be emphasised that the results are preliminary, especially those for 1959. Two important confusing factors are present: for 1959 the diagnosis of paralytic poliomyelitis has been accepted although revision of the diagnosis in some cases is probable at the 60-day follow-up report; and there is considerable heterogeneity in the immunisation status of the population. Thus, a protection-rate calculated on the basis of the overall national immunisation-rate may overemphasise the protective effect of vaccine for poorly vaccinated population subgroups. Similarly, both the national immunisation surveys were carried out in September, which may boost the apparent effectiveness, since unvaccinated people who succumb early in the year would count in the unvaccinated attack-rate, yet those who escaped paralysis in an early epidemic and were subsequently vaccinated would be counted as vaccination successes. The effect of errors of diagnosis would be mainly to include cases presenting with paralysis which were not due to poliovirus. This source of error might, therefore, to some extent counterbalance the effect of different vaccination-rates. It is probable, however, that some cases of apparently non-paralytic poliomyelitis would have to be added to the paralytic group after follow-up. There is some evidence that the viruses isolated from both paralytic and non-paralytic cases are less likely to be poliovirus (and more likely to be other enteroviruses) in vaccinated than in unvaccinated people. LENNETTE et al.[12] report that poliovirus was isolated from 81% of unvaccinated patients with paralytic poliomyelitis under 5 years of age and other enteroviruses from 2%, whereas the isolation-rate

1. Francis, T. et al. *Amer. J. publ. Hlth*, 1955, **45**, supplement.
2. Medical Research Council, *Brit. med. J.* 1957, i, 1271.
3. Paul, J. R., Riordan, J. T., Melnick, J. L. *Amer. J. Hyg.* 1951, **54**, 275.
4. Lennette, E. H., Schmidt, N. J. *ibid.* 1957, **65**, 210.
5. Salk, J. E. *Ann. intern. Med.* 1959, **50**, 843.
6. Dane, D. S., Dick, G. W. A., Briggs, M., Nelson, R. *Brit. med. J.* 1958, ii, 1187.
7. Salk, J. E. *J. Amer. med. Ass.* 1959, **169**, 1829.
8. Barr, R. N., Bauer, H., Kleinman, H., Johnson, E. A., da Silva, M. M., Kimball, A. C., Cooney, M. K. *ibid.* 1959, **170**, 893.
9. Fox, J. P., Gelfand, H. M., Leblanc, D. R., Rowan, D. F. *Amer. J. publ. Hlth*, 1958, **48**, 1181.
10. Horstmann, D. M., Niedermann, J. C., Paul, J. R. *J. Amer. med. Ass.* 1959, **170**, 1.
11. C.D.C. Poliomyelitis Surveillance Report, Nov. 30, 1959, no. 191.
12. Lennette, E. H., Magoffin, R. L., Schmidt, N. J., Hollister, A. C., Jr. *J. Amer. med. Ass.* 1959, **171**, 1456.

was 36% for polioviruses and 21% for enteroviruses in infants who had had two or more doses of vaccine.

Although the exact figure of effectiveness may be subject to revision, it is unlikely that it will prove seriously wrong since it is confirmed in a preliminary study of a major outbreak in Des Moines. The estimates of vaccine effectiveness exceed 85% for three doses for 3 separate population groups (Negroes and lower and middle socio-economic white groups), based on immunisation surveys early in the epidemic. The mere concentration of cases in the least vaccinated groups—for example, the majority of cases were in the 0–4 year age-group and in Negroes (in the whole U.S. the rate for Negroes is twice that in whites and in localised epidemics is up to 15-fold higher)—provides prima-facie evidence of high vaccine effectiveness.

It seems, therefore, that there are good grounds for believing that the killed vaccine has proved highly effective, but that immunisation programmes have proved less so. Some of the proponents of attenuated vaccine have argued that the capacity of these attenuated strains to spread in the community and therefore to vaccinate involuntarily some of those reluctant to accept parenteral vaccine might be a positive advantage. Moreover, they point out that killed vaccine has failed to halt the progress of several outbreaks,[13] and they contend that attenuated vaccine may well be effective under these conditions, not only by producing antibodies more rapidly but also by producing interference in the alimentary tract before active immunity is acquired. Indeed, it has been suggested that epidemics may end not by exhaustion of susceptibles but by the emergence of attenuated viruses. All this is, for the moment, supposition. The best way of combating an epidemic of poliomyelitis is probably the method of passive and active immunisation found so successful for diphtheria.[14] It is known that gamma-globulin is effective in preventing poliomyelitis [15]; indeed, when used for treatment, gamma-globulin of very high titre has mitigated the severity of experimental poliomyelitis in monkeys.[16] Combined gamma-globulin and poliovaccine, perhaps in larger doses,[17] should therefore prove effective.

Recently MELNICK and his colleagues [18] examined some of the candidate strains for inclusion in attenuated vaccine. They found both Sabin and Lederle strains to be more virulent than expected. They also found evidence that Sabin strains (which were the most attenuated) could undergo mutation to substantially greater virulence during passage in man. The difficulties of conducting an adequate trial of safety when virulent virus causes only 1 clinical case in 100–500 infections are considerable. There are also formidable technical difficulties of manufacture to face in order to establish consistently safe vaccine when the virus is mutable and the tissue used to cultivate it is potentially contaminated with numerous viruses.[19] These viruses, except virus B, which is a fatal human pathogen, are of unknown effect in man. The remarkable properties of the newly discovered S.E. polyoma [20] virus should perhaps be a warning against dismissing these viruses from consideration as human pathogens. In view of these manufacturing and testing difficulties, the great economies which it was hoped might follow from the use of living vaccine may prove illusory; but the difficulties have been no deterrent to the mass programme already completed, particularly in Russia and Eastern Europe. In Russia, where Sabin strains have been used, over 10 million people have received all three types of virus; and neither here nor elsewhere has there been any suggestion that poliomyelitis has been caused by any of the strains of attenuated virus. The attenuated vaccine will probably prove effective provided there is not too much interference with the establishment of the poliovirus infection by other enteroviruses, as has been noted, for example, by HORSTMANN et al.[21] MELNICK et al., however, plead for caution in the development of attenuated vaccines. The introduction of killed vaccine required caution, and yet disaster was not wholly avoided: greater caution is called for in introducing a vaccine known to be able to spread uncontrollably in the community. And the need for care is further underlined by the apparently reassuring figures of the efficacy of killed vaccine. It may be that killed vaccine can be made more widely acceptable by the use of combined antigens, which are being effectively given in Canada [22]; and this would also have advantages in reducing the number of injections—a change that would be attractive to children, mothers, doctors, and the Chancellor of the Exchequer.

Breech Presentation and Delivery

UNDER the most favourable circumstances fœtal loss associated with breech delivery is very low. COX [23–25] has shown that at the Liverpool maternity hospital the fœtal mortality in uncomplicated cases has fallen steadily until now several resident obstetricians from that hospital can claim large personal series of deliveries with a fœtal loss below 1·5%. These excellent results come from a teaching hospital which has long taken great interest in the management of breech delivery. It is encouraging to learn from DALEY and MICHAEL [26] and HAY [27] that in non-teaching hospitals, even where breech deliveries are carried out by different people over the years, equally good results are attainable. To some extent such results reflect a tradition passed from one generation of resident staff to another; but much of the credit must lie with the senior consultant staff who are ultimately responsible for standards. It would be unrealistic to claim that hospital management of breech delivery is generally associated with such good results,

13. Poos, R. S., Nathanson, N. *ibid.* 1956, **162**, 85.
14. Fulton, F., Taylor, J., Wells, A. Q., Wilson, G. S. *Brit. med. J.* 1941, ii, 759.
15. Hammon, W. World Health Organisation Monograph Series, 1955, no. 26, p. 357.
16. Liu, O. C., Carter, J. E., Sanders, B. E., Smith, E. C., Hampil, B. *Brit. J. exp. Path.* 1959, **40**, 133.
17. Baron, S., Barnett, E. V., Burch, B. L., Lynch, J. M., Ehrmantraut, W. R. *New Engl. J. Med.* 1959, **260**, 966.
18. Melnick, J. L., Benyesh-Melnick, M., Brennan, J. C. *J. Amer. med. Ass.* 1959, **171**, 1165.
19. Hull, R. N., Minner, J. R., Smith, J. W. *Amer. J. Hyg.* 1956, **63**, 204.
20. Stewart, S. E., Eddy, B. E. Perspectives in Virology: p. 245. New York, 1959.
21. Horstmann, D. M., Niedermann, J. C., Riordan, J. T., Paul, J. R. *Amer. J. Hyg.* 1959, **70**, 169.
22. Wilson, R. J., Moss, G. W. O., Potter, F. C., MacLeod, D. R. E. *Canad. med. Ass. J.* 1959, **81**, 450.
23. Cox, L. W. *J. Obstet. Gynæc. Brit. Emp.* 1950, **57**, 197.
24. Cox, L. W. *ibid.* 1955, **62**, 395.
25. Cox, L. W. *N.Z. med. J.* 1957, **51**, 370.
26. Daley, D., Michael, A. M. *J. Obstet. Gynæc. Brit. Emp.* 1953, **60**, 492.
27. Hay, D. *ibid.* 1959, **66**, 529.

but the available evidence suggests that confinement in hospital is safer than at home. Cox,[23] in his account of breech delivery in Liverpool in 1933–49, reported a fœtal mortality of 20% among 120 cases of uncomplicated breech delivery carried out by midwives in the patients' homes: this despite the fact that the midwives were well trained in the Liverpool technique of delivery. It is impossible for anyone, single-handed, in domiciliary surroundings to compete with the results obtained by a team in a hospital labour ward. Nevertheless, some doctors and midwives still consider that a multiparous breech delivery can safely be conducted at home. This is a dangerous belief, for there is good evidence [23 26 28–30] that the risk to the fœtus is greater in multiparous than in primiparous breech delivery.

In order to assess fœtal mortality associated with breech delivery, Cox and others have excluded from their final figures cases complicated by such factors as placenta prævia, twin pregnancy, prematurity, and prolapse of the cord. Although this arrangement is helpful, not all workers agree about which cases should be considered "complicated" and therefore excluded: some maintain that prolapse of the cord, contracted pelvis, or long labour should be regarded as part of the intrinsic risk to the fœtus. The Royal College of Obstetricians and Gynæcologists [31] gave some guidance on this point in 1948, but there is need for further clarification.

Opinion remains divided on the advisability of external version. Twenty-five years ago WRIGLEY [32] reported a fœtal mortality of 13% when the manipulation was applied under anæsthesia: today the figure is likely to lie somewhere between 1 and 2%.[33 34] Without anæsthesia the risk to the fœtus is significantly less.[35–37] In modern obstetric practice, where fœtal survival in uncomplicated breech delivery can be 98%, the place of external version, particularly under anæsthesia, must be reviewed very carefully. When the patient is to be delivered in a large maternity unit by a skilled team much can be said for WHITE's [30] view that external version should be reserved for patients with slight or moderate pelvic contraction. When external version fails and there is some doubt about the fœtal-pelvic relationship, an important decision about the mode of delivery has to be made. Some obstetricians, with X-ray confirmation of even minor pelvic contraction, would favour elective cæsarean section; but where the disproportion is borderline the majority would probably be prepared to allow a trial of labour. The experienced observer can learn much, under these circumstances, from the pattern of uterine contractions and the progress of labour. With good pains and steady descent of the breech to the pelvic outlet there is every likelihood of a safe vaginal delivery. Abnormal uterine action and failure of the breech to advance point to significant disproportion and the need for cæsarean section. HAY, in his series of cases from St. David's Hospital, Bangor, reports that cæsarean section was carried out in 16% and suggests that this is in keeping with modern obstetric practice. In fact, the need for cæsarean section in breech presentation will vary from one hospital to another. Hospitals deal with selected clinical material, and the rate of cæsarean section will depend on the ages, stature, and parity of the patients and the weights of their babies and is likely to be high when there are many emergency admissions. Study of a total community would give a much truer picture of the management and results of breech presentation in any particular area and would make valid comparisons possible. Unfortunately, there is at present little enthusiasm for such an epidemiological approach to obstetrics.

The survival and well-being of the baby depend largely on the judgment and manipulative skill of the person who conducts the delivery. The best results for mother and baby will certainly be obtained in a well-run maternity hospital where obstetrician, anæsthetist, and pædiatrician work as a team in favourable surroundings. But domiciliary practice will always include cases of breech presentation undiagnosed before the onset of labour. When the diagnosis is made early in labour there is everything to be said for transferring the patient to a suitable hospital. When the presentation is recognised late in labour, this should be regarded as an emergency and the obstetric flying-squad summoned.

28. Cutts, R., Abbas, T. M. *Edinb. med. J.* 1951, **58**, 35.
29. Redman, T. F. *Brit. med. J.* 1950, i, 814.
30. White, A. J. *J. Obstet. Gynæc. Brit. Emp.* 1956, **63**, 706.
31. Royal College of Obstetricians and Gynæcologists. *ibid.* 1948, **55**, 478.
32. Wrigley, A. J. *Brit. med. J.* 1934, i, 891.
33. Peel, J., Clayton, S. G. *J. Obstet. Gynæc. Brit. Emp.* 1948, **55**, 614.
34. Freeth, D., Macvine, J. S. *Brit. med. J.* 1951, ii, 881.
35. Ryder, G. H. *Amer. J. Obstet. Gynec.* 1943, **45**, 1004.
36. Siegal, I. A., McNally, H. B. *Sth med. J.* 1951, **44**, 942.
37. Macafee, C. H. G., McClure, H. I. *Brit. med. J.* 1937, ii, 1117.

Ultrasonics in Ménière's Disease

THE symptom-complex of paroxysmal rotatory vertigo with deafness and tinnitus has long been recognised as a disabling condition. PROSPER MÉNIÈRE brilliantly deduced its pathology by correctly interpreting the work of his colleague FLOURENS, who in 1842 observed disorders of equilibrium in pigeons after injury to the semicircular canals. As early as 1883 WOAKES [1] advanced the hypothesis that it was associated with increased intralabyrinthine tension—a hypothesis which was finally confirmed in 1938 by HALLPIKE and CAIRNS [2] in their classic description of the distended endolymphatic system in the labyrinth affected by Ménière's disease.

No wholly satisfactory method of treatment has yet been devised. This failure is due to several reasons: the labyrinth is enclosed in a capsule of hard compact bone within the petrous pyramid, which makes any direct observations on its delicate neuroepithelium very difficult; the disease itself is never lethal, so opportunities for postmortem study are rare; and assessment of therapeutic results is difficult because spontaneous remissions are common and may last for many years. Mental strain is said to foster attacks, possibly through sympathetic-parasympathetic imbalance resulting in hydrops of the labyrinth. But, while emotional stress is often evident in Ménière's disease, this is to be expected in a condition where a fit person is suddenly struck down with acute vertigo at unpredictable moments. In treatment simple sedation, vasodilators, histamine, vitamins, diets, and anti-histamine drugs are all used singly or in combination. Relief of symptoms followed by remissions is achieved in a high proportion of cases; but in most

1. Woakes, E. *Brit. med. J.* 1883, i, 801.
2. Hallpike, C. S., Cairns, H. *Proc. R. Soc. Med.* 1938, **31**, 1317.

published series gradual deterioration of hearing in many cases, and development of the disease on the other side in some, have been noted. Surgery is indicated when medical treatment has failed, and should be undertaken without undue delay. Three main types of operation are in use: intracranial section of the vestibular fibres of the eighth cranial nerve; destruction of the labyrinth; and sympathectomy. In most cases the paroxysmal vertigo is relieved by the first two methods. The hearing is totally destroyed by any direct operation on the vestibular end-organ, and it is often damaged by partial section of the eighth nerve. Sympathectomy was introduced to preserve the hearing, but it does not always control the vertigo. As Ménière's disease becomes bilateral in 10–30% of cases, great efforts have been made to devise treatment that is effective and yet does not impair the hearing.

The possibility of applying ultrasonic frequencies to a restricted part of the inner ear, without damaging adjacent structures, was demonstrated by KREJCI and BORNSCHEIN [3]; and LUMSDEN [4] has now described his experience of ultrasonic ablation of the vestibular end-organ. Ultrasonic waves do not pass from air to a solid or liquid medium (or vice versa) because they are reflected at the interfaces. The bony external semicircular canal is therefore exposed surgically and ultrasound applied directly to the canal. The irradiation is directed so that both the cochlea and the facial nerve are avoided. Ultrasound may act by means of its mechanical, thermal, or chemical effects; but its precise mode of action on the labyrinth has not yet been established: this is one objection to its routine use. Undoubtedly, however, tissue destruction results from the application of suitable ultrasonic doses; and this constitutes a difficulty in clinical practice, where dosage must be based on the inexact signs of nystagmus and on previous experience. ARSLAN [5] has reported the biggest series hitherto: in six years' follow-up 95% of patients were free of acute vertigo and the majority had unimpaired hearing. LUMSDEN found that in the first few weeks after operation modified attacks of vertigo might occur while the degeneration of the labyrinth became complete; continued vertigo usually denoted an inadequate dose. A second application sometimes controlled the symptoms. Facial palsy is the most important complication, but in all the reported cases spontaneous recovery has ensued. The effect of ultrasound on persistent tinnitus is somewhat unpredictable, but ARSLAN seems to have had more success than some other workers.

A good deal of work on the effects of ultrasound in Ménière's disease remains to be done. But, though still in the experimental stage, ultrasonic ablation of the labyrinth is already worth considering in cases with good hearing that do not respond to medical treatment, or where the patient is already deaf in the other ear from previous disease, labyrinthectomy, or other causes. Ultrasound may eventually prove superior to all other forms of treatment.[6] [7]

3. Krejci, F., Bornschein, H. *Arch. ital. Otol.* 1951, **62**, 1.
4. Lumsden, R. B. *Scot. med. J.* 1959, **4**, 519.
5. Arslan, M. *Sci. med. ital.* 1958, **7**, 301.
6. Dubs, R. *Pract. oto-rhino-laryng.* 1957, **19**, 401.
7. Altman, F., Waltner, J. G. *Arch. Otolaryng., Chicago*, 1959, **69**, 7.

Annotations

SEWAGE AND THE BATHER

FOR some years concern has been expressed in Parliament and in the Press about the risk of contracting infectious diseases (and especially poliomyelitis) by bathing in seawater polluted by sewage. A committee of the Public Health Laboratory Service has for some years been inquiring into this danger and its findings have now been published in a scientific report [1] and an abbreviated version thought suitable for politicians and journalists.[2] Having reviewed evidence from many sources, the committee can say without qualification that there are no grounds for thinking that bathing in the sea involves any appreciable risk of diseases.

The most popular beaches are those adjacent to large towns, and almost all these towns discharge their sewage into the sea. Most samples of water from these beaches show clear evidence of fæcal pollution and some contain *Salmonella spp.* in small numbers. Technical difficulties make the hunt for poliovirus very difficult, but there is no reason to doubt its presence along with the other fæcal organisms. The chief virtue of discharging sewage into the sea is that it is quickly diluted; and to this dilution the bathers owe their freedom from infection. Except for *S. typhi*, the dose of salmonellæ needed to produce disease in man is large; and, for reasons not yet fully understood, human pathogenic bacteria do not survive very long in seawater. On the epidemiological side the evidence is scanty—partly because the person who has bathed has probably also eaten ice-cream, winkles, and fish-and-chips—to say nothing of looking at the peepshows on the pier.

One of the major tasks of the committee was the collection of bacteriological data—counts of coliform organisms and fæcal coli—from many beaches. The interpretation of these is difficult. No two beaches and no two sewage outfalls are alike. The vagaries of local tidal currents are unpredictable without long experience and exact tests with floats or radioctive tracers. Dilution is not immediate and its efficacy will obviously depend on the distance of the sampling-point from the outfall and upon the temporary effects of wind and waves. At no point within the range of the sewage outfall can the water be considered as a homogeneous fluid, and a difference of an hour (in relation to high water) can give very different bacteriological results. For this reason the committee rejects the idea of a standard of bacteriological purity for bathing-beaches similar to that used for drinking-water. Such standards exist in a few places in the U.S.A., and there is no evidence that they have had any effect on the public health or that they are enforceable. The bacteriological survey has, however, some uses. Sampling at short intervals along the beach, continued for many months in all sorts of weathers, will give a reasonable idea of the amount of fæcal pollution and may be essential in judging the need for a new outfall or assessing the results of such an improvement. But—like a bacteriological finding in clinical medicine—it means very little unless it is considered in conjunction with all the other factors involved, and a few unplanned and irregular tests can only be misleading. To compare the health-giving properties of Brinyville and Foulwater Bay by such tests is dishonest.

1. Report. *J. Hyg., Camb.* 1959, **57**, 435.
2. Medical Research Council Memorandum no. 37. H.M. Stationery Office. 1959. Pp. 24. 2*s.* 6*d.*

So far so good; and it is satisfactory to know that one potential source of risk to health has been given an approximate quantitative value. We hope, however, that this report will not be used as an excuse for making our beaches even more foul than they are today. The population of seaside towns is increasing above the average rate, and more people spend more time on the beach. Because fæces and toilet-paper are not yet common objects of the seashore is no excuse for a practice which is almost always dictated by cries for economy. It is true that a greater danger to health and natural beauty comes from the pollution of our estuaries (about which the committee was not concerned). The dilution factor in an estuary is variable, affected by wind, water, and the flow of fresh water, and usually insufficient. An oversight by the legislators of the last century allowed estuaries to be treated as the open sea, and the result is only too obvious in the Thames, the Dee,[3] the Tyne, and fifty other rivers. As a factor in robbing the water of oxygen, sewage is ancillary to industrial effluents, and the result is a fluid which will support no form of life—except bathers. (There is no more popular bathing-place in London than the plage just above Tower Bridge.)

The committee did not consider the dangers of bathing in fresh water, and about this we know very little. The Thames Conservancy forbid the discharge of excreta from any boat on their waters and enforce this by-law strictly. Other bodies with similar problems should follow the Conservancy's example. The danger of catching typhoid by bathing in the Norfolk broads may be small, but nobody knows how big it is. We must be grateful to this committee for pointing out the way in which these and many similar problems can be tackled.

IMMUNOLOGICAL UNRESPONSIVENESS

RECENT interest in the possible role of autoantibodies in the pathogenesis of some human diseases has been a considerable stimulus to work on fundamental processes of antibody production. In this category is the study by Crampton, Frankel, and Rodeheaver [4] on the mechanism of immunological unresponsiveness. Such a state of specific unresponsiveness can be induced in several species of animal by repeated injections of large amounts of the appropriate antigen [5 6]; and by the use of antigens labelled with radioactive iodine Crampton and his colleagues sought to demonstrate the difference, if any, in distribution of the antigen in responsive and unresponsive animals. No such differences were detected, the antigen in both series of animals being found in intracytoplasmic granules in the liver and spleen. Crampton et al. have, therefore, suggested that the condition of immunological unresponsiveness may result from the destruction of the specifically stimulated cells by an intracellular antigen-antibody reaction. As long as an excess of antigen is made available it is presumed that sufficient free antigen will be contained in the antibody-producing cells to encompass their own destruction. With the relatively minute quantities of antigen usually used to stimulate antibody formation the quantity of antigen within some, at least, of the stimulated cells is presumably too small to be lethal.

The distinction between immunological unresponsiveness and immunological tolerance is noteworthy: unresponsiveness is brought about and maintained by repeated injections of large quantities of antigen at almost any period of life: tolerance is a more or less permanent state induced by the injection of living cells within a very short period of birth.[7] Since the persistence of tolerance also requires the survival of the injected foreign cells or their descendants the final mechanism may well be the same—namely, self-destruction of the specifically stimulated cell, the result of intracellular reaction of antigen and antibody.

A particularly attractive feature of this hypothesis of Crampton et al. is the explanation that it affords of the differences between a primary and a secondary response. Thus, following primary stimulation by a small amount of antigen the antibody that subsequently appears in the plasma is the product of those specifically stimulated cells that have survived any intracellular antigen-antibody reaction. Whatever is the precise nature of these cells when first they make contact with antigen they subsequently acquire the cytological characteristics of plasma cells, and thus have apparently lost the ability to take up antigen intracellularly. Since they continue to secrete specific antibody protein it is reasonable to assume that they are still capable of reacting specifically with any future access of antigen. It is postulated, however, that such a surface interaction results, not in death, but in stimulation to proliferation. The secondary response is therefore characterised by both its speed and its magnitude.

A slightly different but even further reaching hypothesis was put forward by Burnet in 1957.[8] This too requires that according to circumstances the antibody-forming cells are killed or excited to reproduce. The recent work of Crampton and his colleagues offers a plausible explanation of the way in which these strikingly different results could be brought about.

THE GAMMA SYSTEM IN MAN

THE gamma system comprises the small-diameter efferent nerve-fibres which originate from small anterior-horn cells, together with the intrafusal muscle-fibres which they supply within the muscle spindles. As Leskell [9] originally showed in cats, this system can change the sensitivity, or bias, of the primary (annulospiral) sensory endings to imposed stretch. Subsequently both the functioning of the gamma system and its supraspinal control have been intensively studied. Apparently, in many postural reflex contractions of striated muscle, nerve impulses are initially routed from the spinal cord via the small efferent fibres to produce a shortening of the intrafusal muscle-fibres. This shortening stretches the primary sensory endings and increases their afferent discharge. The resultant enhanced bombardment of large anterior-horn cells leads to contraction of the extrafusal striated muscle-fibres, which diminishes the spindle afferent discharge. The primary sensory endings here operate as null detectors, discharging afferent impulses at a rate which is proportional to the differing lengths of the intrafusal and extrafusal muscle-fibres. This conception of the muscle-spindle's function enlarges the earlier view that the spindle acted merely as a detector of muscle stretch, though both of these activities ultimately depend on stretch of the primary sensory ending. Merton [10] further suggested that

3. *Lancet*, 1959, i. 927.
4. Crampton, C. F., Frankel, F. R., Rodeheaver, J. L. *Nature, Lond.* 1959, **184**, 873.
5. Dixon, F. J., Maurer, P. H. *J. exp. Med.* 1955, **101**, 245.
6. Boyd, W. C. Fundamentals of Immunology. New York, 1956.
7. Billingham, R. E., Brent, L., Medawar, P. B. *Nature, Lond.* 1953, **172**, 603.
8. Burnet, F. M. *Aust. J. Sci.* 1957, **20**, 67.
9. Leskell, L. *Acta physiol. scand.* 1945, **10**, suppl. 31.
10. Merton, P. *in* The Spinal Cord (edited by J. L. Malcolm, J. A. B. Gray, G. E. W. Wolstenholme, and J. S. Freeman). London, 1953.

the gamma system might play an essential part in the execution of certain willed movements. He postulated that descending impulses from the supraspinal centres controlling willed movements might be routed to the small anterior-horn cells and thus produce willed contraction of striated muscles over the same pathways as those of postural reflexes.

From all this work it seemed that the gamma system might be of considerable importance in man. Many of the observations on man are based on a finding of Hoffmann [11] that the medial popliteal nerve may be electrically stimulated in such a way as to produce a pure reflex contraction of the gastrocnemius-soleus muscle-group. This H reflex [12] was thought to follow the same reflex pathway as the ankle-jerk, but to differ from the tendon reflex in so far as the muscle-spindles (and the associated gamma efferents) were removed from circuit. Differences in the responses of the ankle-jerk and the H reflex could thus be equated with the degree of activity in the gamma system.

Sommer [13] observed that Jendrassik's reinforcement potentiated the ankle-jerk while leaving the H reflex unaltered; the experiments were repeated by Paillard,[14] and reinforcement has been ascribed to enhanced activity of small motor-fibres leading to increased sensitivity to stretch of the primary spindle-endings. Similarly Buller [15] suggested that the hyperreflexia of early hemiplegia is due to resetting of the muscle-spindles on the abnormal side, and Benson [16] has argued that some labyrinthine reflexes are effected via the gamma system. The validity of all these arguments rests on the assumption that the central reflex pathways of the ankle-jerk and the H reflex are identical. But Magladery and Teasdall [17] have shown that in man probably neither the ankle-jerk nor the H reflex pursue purely monosynaptic paths, and they have questioned whether the ankle-jerk and H reflex do follow identical central pathways. If the pathways are different—if, for example, the spinal pathway subserving the ankle-jerk includes an interneurone which is not also activated during elicitation of the H reflex—then supraspinal control of that intraneurone [18] might explain the differences between the tendon-jerk and H-reflex responses attributed by Sommer,[13] Buller,[15] and Benson [16] to gamma-system activity. Thus, while the observations of these three workers suggest that the gamma system is functionally important in man, they do not prove it.

Further indirect evidence of the existence of tonic gamma-system activity during the waking state is provided by the observation of Buller and Dornhorst [19] that local infiltration round the medial popliteal nerve with cinchocaine abolishes the ankle jerk while leaving the H reflex unaltered. By analogy with the differential gamma-fibre blocks produced in the cat with procaine,[20] Buller and Dornhorst suggested that they had selectively blocked the gamma efferent fibres to the muscle-spindles supplied by the medial popliteal nerve. If this is correct, it would seem that in the waking state the intrafusal muscle-fibres are continuously under gamma control, and therefore probably accessible to reflex or supraspinal control.

All these observations on man have been concerned with the tendon-jerk. The gamma system also takes part in determining the static stretch reflex, which is estimated clinically as muscle tone. That the tendon-jerks and muscle tone may vary independently is known from clinical experience, and has been clearly shown by Hammond.[21] The explanation of this independence probably lies in the separate supraspinal control of synapses on the central pathway for tone which do not form part of the spinal pathway of the tendon reflex. Such synapses may be at interneurones and/or Renshaw cells. While the discharge from the muscle-spindle (itself determined by gamma activity) is important in determining both the tendon reflex and muscle tone, differences in the intraspinal pathways of these two reflex arcs allow independent supraspinal control.

Thus, in man there is indirect evidence that the gamma system plays a part in both the phasic and the static reactions of the stretch reflex. It seems likely that gamma efferent activity is maintained throughout the waking state and may be modified as part of normal postural reflex activity, and also as a result of damage to the central nervous system. The part played by the gamma system in willed movement is still unknown.

11. Hoffmann, P. *Z. Biol.* 1920, **70,** 515.
12. Magladery, J. W., McDougal, D. B. *Bull. Johns Hopk. Hosp.* 1950, **86,** 265.
13. Sommer, J. *Dtsch. Z. Nervenheilk.* 1940, **150,** 249.
14. Paillard, J. Reflexes et regulations d'origine proprioceptive chez l'homme. Paris, 1955.
15. Buller, A. J. *Lancet*, 1957, ii, 1262.
16. Benson, A. J. *J. Physiol.* 1959, **146,** 37P.
17. Magladery, J. W., Teasdall, R. D. *Bull. Johns Hopk. Hosp.* 1958, **103,** 236.
18. Eccles, R. M., Lundberg, A. *J. Physiol.* 1959, **147,** 565.
19. Buller, A. J., Dornhorst, A. C. *ibid.* 1958, **145,** 12P.
20. Matthews, P. B., Rushworth, G. *ibid.* 1957, **135,** 263.

NEW YEAR HONOURS

IN recognition of his presidency of the Royal College of Surgeons, Sir James Paterson Ross receives a baronetcy. Even before his election, Sir James did much for the college in the congenial role of dean of the Institute of Basic Medical Sciences; and in the difficult period of financial reconstruction that has coincided with his term of presidential office the college has been fortunate in having at its head a man so much respected alike as a surgeon, as a teacher, and as a person. Similarly, as president of the Royal College of Obstetricians and Gynæcologists, since 1957, Prof. Andrew Claye has given a great deal of time and thought to its development, and his knighthood will give pleasure both on public and on personal grounds. Dr. Ivan Magill, who is promoted to a knighthood in the Royal Victorian Order, is one of the innovators who have created modern anæsthesia; and by his tubes, his laryngoscope, and his rebreathing bag his name is known wherever this art and science are practised. As a practical prophet, he is very far from being without honour in his own country. Prof. Derrick Dunlop not only has been chairman of the British Pharmacopœia Commission, and much else that officially justifies his knighthood, but also is a great Edinburgh personality and memorable teacher. Moreover, unlike so many knights nowadays, he lives in a real castle. In Australia, Sir Charles Blackburn, who is created K.C.M.G., was knighted in 1936 and has been chancellor of the University of Sydney since 1941: he is consulting physician to the Royal Prince Alfred Hospital. Of the knights bachelor, Prof. Edward Ford became director of the School of Public Health and Tropical Medicine in Sydney in 1947, having done much work in the Army which his colleagues rated especially high; and Dr. W. W. S. Johnston, who has a fine record during and after both world wars, has been consulting physician to the Royal Melbourne Hospital, and chairman of the Melbourne Permanent Postgraduate Committee, for four years. Prof. J. P. Walsh, now K.B.E., is dean of the University of Otago Dental School.

The remainder of the list published on p. 106 contains the names of many other medical men and women who are held in high regard by those who work with them and by those for whom they work.

21. Hammond, P. H. *ibid.* 1956, **132,** 17P.

Special Articles

HOTELS OR HOSPITALS?

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THERE can be no dispute concerning the national need for new hospitals. Conflict of view on what form they should take, and what function they should serve, may provoke original thought and avoid perpetuating unfortunate and costly errors. It would be flippant to suggest that the Government should build expensive hotels in which hundreds of thousands of citizens could live expensively but free (in so far as anything paid for by taxes is free) for such varying times as they or their doctors considered their health was below par. Unfortunately, however, there is a real danger that many of the millions pledged for hospital construction may provide hotels instead—and very expensive ones! The name "St. Trinian's Hospital" rather than "Hotel Sans Souci" in neon lights over the palatial entrance to a modern skyscraper will not alter the use made of its beds.

Intelligent planning and bold but reasoned experiment are necessary to build a hospital service worthy of the latter half of the 20th century and not a mere chromium-plated replica of a system now outmoded. A revolution in building and administration must be preceded by a revolution in thought. Most people find revolutions disturbing; but, in fairness to Governments that build and citizens who pay, a warning seems justified. To clamour for the spending of £750 million is foolish unless guidance is given on how it may best be spent. Wise planning and spending could result in Great Britain leading the world in a new concept of hospital service.

Great advances in medicine have transformed the legitimate demands that should be made on hospitals. Diagnosis is more rapid and accurate, and to an increasing extent is, or should be, an outpatient procedure, whereas previously it was not unusual for patients to occupy hospital beds for days and even weeks "under observation" while a diagnosis was made. (Although the justification now seldom exists, the practice is not entirely obsolete.) Treatment is now more precise. Where patients were once admitted with acute infections from which many died and others required long periods of intensive nursing, most are now treated effectively at home by the family practitioner. Developments in anæsthetic and surgical techniques have revolutionised surgery. The patient is no longer an invalid for weeks or months after a simple abdominal operation. He serves tea to his fellow patients a few days after a bowel resection or a lobectomy, and feels the better for it! Emphasis on positive health and rapid rehabilitation is increasing. The illness or the operation is an unfortunate interlude to be forgotten as soon as possible, and the whole hospital service should be so designed and maintained as to facilitate this process.

VALUE FOR MONEY

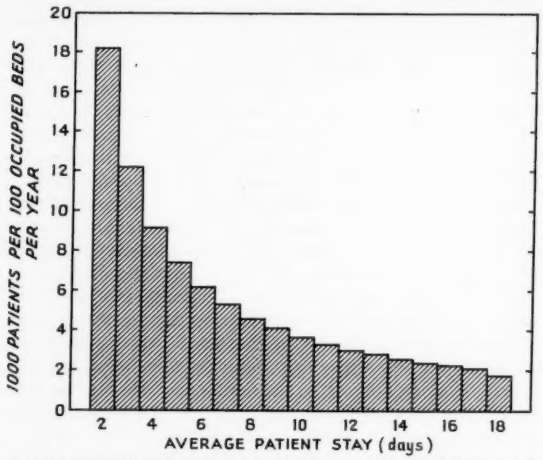
New techniques can demand highly specialised and expensive equipment and staff, and add to capital and maintenance charges. This is one excuse made for the high cost of the present hospital service, and will doubtless be used to justify greater expenditure in the future. The excuse is only partly valid. Accumulating evidence in published estimates suggests that it is widely accepted that hospital construction must be relatively expensive, even when special facilities and equipment are either not required or are minimal. For example the cost of new "acute" hospitals, planned or recently built, varies within a range of £3000 to £6000 a bed. Even the lower figure is nearly three times the estimated cost of accommodation per guest in new luxury hotels now being built in the London area. It is true that hospital charges expressed in this way include the cost of theatre suites, expensive equipment, nurses' accommodation, &c.; but it is also true that with hotels the estimate provides for public rooms, ballrooms, restaurants, private bathrooms with every bedroom, and the other amenities considered essential in a modern hotel of international repute. This comparison is not to suggest that one is too expensive or the other surprisingly cheap, for only those with an intimate knowledge of all the factors associated with modern building could evaluate the two. It should however emphasise the great cost of a modern acute hospital and the relative expense of simpler institutions used in the hospital service.

If hundreds of millions sterling are to be spent on building, it is essential that the Government and the taxpayer receive value for the money. Expensive equipment should be used as far as possible solely for the purpose for which it was designed, and to the maximum of its capacity: industry achieves efficiency in this way. A surgical theatre suite makes its contribution to each patient in a relatively short time varying from minutes to hours. Too often, however, theatre and other expensive facilities are limited in the work they could do because beds are fully occupied. In the meantime waiting-lists grow with all the associated implications of disordered homes and absence from work. The generally accepted solution to the waiting-list problem appears to be "more beds". This would mean bigger hospitals, or more of them, with a corresponding increase in the cost of the hospital service. To adopt this policy would be short-sighted, for there are weighty arguments to support the view that a more efficient service could be provided with smaller acute hospitals and fewer beds. Factors already discussed are decreasing the demands made on certain sections of hospital beds at present available in fever and other hospitals. Many of these beds could now be used to advantage as suggested later.

STAY IN HOSPITAL

With these general concepts in mind, study of the Ministry of Health national costing returns for 1958 discloses some startling facts. Even the official definitions used are relevant. An "acute" hospital is one in which *not more than 15%* of the beds are "allocated to the excluded departments". This means set aside for the use of chronic sick and other categories of non-acute conditions. A "mainly acute hospital" can have *up to 40%* of its beds allocated to these purposes. This should be remembered when one considers the equipment, staff, and expense of a modern acute surgical or medical unit. To serve hot dogs at a shilling a time in the Savoy Grill would be uneconomic, and so is the established practice of keeping convalescent patients in acute hospital beds. What is urgently needed is a reappraisement of what is meant by a convalescent patient.

The 1958 report records that hospital A (a famous London teaching hospital of about 700 beds) had an average stay per patient of eighteen days. Hospital B (a teaching hospital of about 400 beds) had an average stay



Graph to correlate the number of patients who could be treated in 100 occupied beds with the average number of days they spend in hospital.

of nine days. There must inevitably be many factors other than the time patients are kept in hospital which differ in the two institutions, but they have this in common that both are general teaching hospitals with special departments, and both have reason to be jealous of the high standard of medical care provided. The 700 beds in hospital A treated just under 14,000 inpatients in the year, while hospital B with 400 beds treated nearly 17,000. If hospital A reduced its average stay per patient to nine days it would double the number of patients treated to 28,000. If these patients were not available it could either close beds and reduce the size of staff, or admit from the waiting-lists of other hospitals working under greater pressure. Furthermore, if hospital A were scheduled for rebuilding, it would be unrealistic to claim that it should be reconstructed as a 700-bed unit unless a reasonable case were made to justify this in terms of increased medical demands expected to be made upon its services.

Conversely, if hospital B (average patient stay of nine days) decided for some reason it would work to a basis of an average stay of eighteen days, it would treat only 8500 inpatients instead of 17,000 as at present. This would increase further its already huge waiting-list to such an extent that a public outcry (though misinformed) would almost certainly demand more beds and more staff. To treat the same number of patients as at present, only with an eighteen-day average stay, it would need to double its size to 800 beds.

This perhaps oversimplifies the position, but the available evidence in hospital and national reports confirms the basic truth of the argument. No London teaching hospital in 1958 had an average stay of less than fourteen days and the range was up to twenty-four. In the provincial teaching hospitals the range was nine to sixteen days. The non-teaching acute hospitals of the Metropolitan area and the country as a whole had a corresponding variation in the average stay of patients. An increase from ten days to twelve days per patient may seem small, but it represents a fall of about 15% in the contribution a hospital has been making and in terms of national figures it is of tremendous importance. The chart demonstrates how the number of patients 100 occupied beds can handle in one year is related to the average length of stay.

A low average figure is not in itself a goal to be aimed at, but it emphasises certain facts which are often overlooked. The patient who stays in hospital a day longer than necessary *uses the hospital as a hotel*. Major discrepancies between the average stay in hospitals of comparable size and purpose are a measure of the extent to which at the present time hospitals are used as hotels. It is ironical that in many cases a patient could be more comfortable, have greater privacy, better food, and more quiet at approximately half the cost if he were in a hotel with several stars to its credit.

Destructive criticism is easy, but a problem as vast and important as the National Hospital Service demands a constructive approach. Any major reform is certain to challenge many traditional concepts and may arouse powerful opposition. Experiment with pilot schemes can be valuable; for once facts prove a contention it is difficult for opposition to survive.

BETWEEN HOSPITAL AND HOME

The phase of acute illness in medical and surgical diseases is now generally short. A period follows of varying length during which there could be no better place in which to recover than at home under the supervision of the family practitioner, provided the necessary facilities exist and the patient and relatives desire it. In America this early return home has been made necessary by the high cost to the patient of hospital care. Hospital costs in Great Britain are also high, and are steadily increasing; but the Welfare State protects most patients from any personal financial strain when, with the acute episode safely over, they prolong their stay and convert the hospital into a hotel. Unfortunately home conditions in Great Britain seldom warrant an early transfer; but with rising standards of living, better housing, and an effectively organised home-help service, it would be reasonable to expect improvements in the future.

A major criticism of the present service is that little thought has been given to the problem of how to bridge the gap between the acute episode and the time when the patient could reasonably return home. Early convalescence is usually spent in wards designed, equipped, and staffed for acute work. In his excellent article on Hospitals for Today and Tomorrow [1] Farrer-Brown referred to a Nuffield Provincial Hospitals Trust survey team's findings that a quarter of the patients in medical beds in a general hospital could have been treated at home or in the outpatient department, and that nearly half remained in hospital longer than was necessary. Those who need the facilities of an acute unit are kept waiting by those who do not.

The solution is obvious. Hospitals designed for acute work should be used for that purpose and *for that purpose only*, with early patient transfer to a simple, quieter, less expensive environment where medical and nursing requirements would be minimal. Emphasis would be on self-help and rapid rehabilitation.

Practical experience of this concept has revealed the advantage of the consultant responsible for the management of the acute phase of the disease retaining control in the convalescent annexe, but there is every reason to explore to an increasing degree cooperation with the family practitioner once patients have been transferred.

The siting of these annexes could well vary according to local conditions. Small towns can no longer have a modern and efficient hospital. (This suggestion may be resented by some but it is an economic and medical fact.)

1. Farrer-Brown, L. *Brit. med. J.* 1959, i, suppl. p. 188.

These towns, however, could be equipped with the new-purpose annexe and in this way allow their citizens to return among friends and relatives a few days after operation, or once the acute phase of illness was over. This would help integrate general practitioners into the hospital service and facilitate continuity of care by the family doctor. In the cities these convalescent annexes could be more closely associated with the acute hospital units, and, where space permitted adequate access to the open air and to gardens, it would probably be more economical to have them close to the acute unit. In the meantime, however, use should be made of empty beds in fever hospitals and chest units.

ADMINISTRATION AND NURSING

A 1000-bed hospital of the type now envisaged would differ from the present 1000-bed hospital in many ways, including nursing and administration. Staffing of the acute unit would need to be generous; otherwise the strain would be too great. In the annexe, however, staffing would be minimal, and all possible use could be made of part-time workers. The scheme suggested could help solve the nursing problem not only of Great Britain but of other countries as well. It should also lead to a reassessment of the great expansion of hospital administrative personnel since the appointed day. The Whitley Council system of paying certain staff on a points-per-bed (or cot) basis might be more efficient under the proposed scheme than under the present one.

It may be argued that this plan would make nurse training harder. If the responsible authorities wish to continue training nurses as at present, there would be weight in the criticism; but the changing face of medicine has modified the conventional pattern of nursing duties. This fact is being too often overlooked, with the result that nurses spend time and energy in badly designed wards carrying unnecessary bedpans, wash bowls, and food dishes to patients who would be much better and much happier attending to their own needs if only facilities existed for them to do so. In their hours of study nurses are trained in medical and surgical detail to an extent which would enable many to compete favourably in examination with medical students, and it is certain that this increased knowledge is not an essential to devoted, sympathetic, and skilful nursing. (It can in fact be a handicap.) In acute wards detailed nursing care is essential, but in the annexes the attention required would be slight. Adequate rest and recreation rooms, ample bathroom and lavatory accommodation, cafeteria feeding, and modern kitchen and cleansing equipment, would reduce domestic staff to a minimum. Conditions would be ideal for nurses from acute units to relax while acting merely in a supervisory capacity during spells off acute duty. The psychological advantage to a patient of being transferred early from the hospital atmosphere of acute wards to the simpler and more relaxed life of the annexe would be considerable.

WARD/ANNEXE BED RATIO

The ideal relation between the number of acute and annexe beds would vary from specialty to specialty and would require considerable preliminary experiment. The greater the number of annexe beds in effective use the cheaper would be the hospital service. From experience of practising these ideas at Oxford we believe that in gynæcology a reasonable relationship would be 30 annexe beds for an acute ward of 24 beds. At no time have the convalescent facilities at Oxford been either adequate or sufficiently stable for a continued practical trial, and the ratio suggested may need adjustment after further experience. Any alteration would probably be to increase the proportion of annexe beds.

DEDUCTIONS FROM OXFORD EXPERIENCE

In the area department at Oxford 39 acute gynæcological beds accommodated 1991 surgical patients in 1958 and have averaged 1814 a year over the past five years. 24 of these beds are at the Churchill Hospital and 15 at the Radcliffe Infirmary. Because of shortage of convalescent beds the practice has been to give the Radcliffe priority over the Churchill in the use of beds available. The result has been that in 1958, with the same consultant staff, 925 operations were performed from the 15 Radcliffe beds, and 1066 from the 24 Churchill beds. With an adequate senior staff and constant use of even the limited convalescent facilities used by the Radcliffe, the Churchill would have been able to operate on at least 1500 patients without being given any extra acute beds. This would have reduced the gynæcological waiting-list from over 600 to practically zero within a year. The next step would be to *reduce the number of acute beds.*

Allowing an average stay of five days in the acute ward for major operative cases (many would require less) and ten in the annexe, a unit of 24 acute beds and 30 annexe beds should be able to treat 1500–2000 patients a year. Those requiring special investigations would be admitted to the annexe in the first instance, be transferred the day before operation, and return a few days later. For this volume of work the 24 acute beds would require theatre facilities for at least three major lists a week, preferably with two theatres available for each. Daily access to a theatre, even if for only an hour, would enable minor cases and "day" cases to be handled in considerable numbers if a few beds were set aside for patients requiring minor procedures such as cystoscopies, pyelograms, and biopsies. Even these demands would occupy less than half the available theatre time. The remainder could be utilised by a comparable surgical unit handling approximately the same number of patients. Thus a basic acute unit of two wards of 24 beds each, and a theatre suite of two theatres with a recovery room, should be able to treat surgically a minimum of 3000–4000 patients a year. The size of the theatre suite would obviously be developed in proportion to the number of acute wards attached, but it will be apparent that a suite of four theatres serving four wards with a total of just under 100 acute beds could on the above figures treat 6000–8000 surgical patients a year. This may well be an underestimate.

To appreciate what this means in terms of present practice, these 100 acute surgical beds with their associated annexe facilities could treat annually at least as many surgical patients as the total of all patients at present admitted to some acute hospitals, teaching and non-teaching, of 300–350 beds. A comparable reduction in the number of acute medical beds at present in use would seem reasonable. The result would be acute hospitals of reduced size and improved efficiency, one indication of which would be the virtual abolition of long waiting-lists.

In this concept of an acute hospital service we should need staff sufficient to use the facilities to full capacity, but there should be flexibility. The idea of a consultant being given x beds on his appointment to a hospital and regarding these as his own for the remainder of his active life, to be increased possibly but never decreased, is outmoded and uneconomic. It is hard to justify consultants (or teams of consultants) in any specialty retaining a considerable number of beds when they have almost no

waiting-list, while the staff in another department struggle in vain against a constantly increasing pressure of work. Admittedly the number of operations competently performed in a session is not the only index of a surgeon's contribution; but we can be pretty sure that two surgeons working as a team will do more than they could if they worked separately—and will do it with less effort. Particularly is this so when the clinical load is heavy and when two theatres are used at one operating session. When one consultant was away, or when pressure of waiting-lists required it, beds might be diverted temporarily from one service to another. These are points which should be decided on grounds of need and common sense rather than privilege or pride.

In the scheme here outlined an essential to success would be efficient teamwork by all concerned—doctors, nurses and administrators—determined to utilise to the full their resources. By so doing they would render the greatest possible service to patients at the lowest possible cost.

To explore the potential advantages, and also the difficulties both foreseen and unforeseen, a pilot trial would be necessary. In terms of the projected £750 million building programme this would be inexpensive, but its results could be far-reaching.

SUMMARY

Medical and surgical advances have changed the demands that can legitimately be made on hospitals. They are not hotels.

Hotels are cheaper than hospitals to build and maintain.

A positive attitude to health should reduce to a minimum the time a patient spends in hospital.

The acute episode of illness is usually short but its efficient hospital treatment is expensive.

Acute beds should be used for acute work only, and should be integrated with relatively inexpensive annexes. Estimates are given of the clinical potential of an acute surgical unit with annexe facilities.

The acute hospital of tomorrow could be much smaller and more efficient than its present counterpart.

An experimental pilot trial is advocated.

NEW YEAR HONOURS

THE list of honours published on Jan. 1 contains the names of the following members of the medical profession.

Baronet

Sir JAMES PATERSON ROSS, K.C.V.O., M.S. Lond., LL.D. Glasg., Hon. F.R.A.C.S.
President, Royal College of Surgeons of England; professor of surgery in the University of London at St. Bartholomew's Hospital Medical School.

K.C.M.G.

Lieut.-Colonel Sir CHARLES BICKERTON BLACKBURN, O.B.E., M.D. Sydney, F.R.C.P., F.R.A.C.P., R.A.A.M.C. retd.
Chancellor of the University of Sydney.

K.C.V.O.

IVAN WHITESIDE MAGILL, C.V.O., M.B., D.A. Belf., F.R.C.S.

K.B.E.

JOHN PATRICK WALSH, M.B. Melb., B.D.SC., F.D.S. R.C.S.
Dean, University of Otago Dental School.

Knights Bachelor

ANDREW MOYNIHAN CLAYE, M.D. Leeds, Hon. M.D. Melb., F.R.C.S.
President, Royal College of Obstetricians and Gynæcologists; professor of obstetrics and gynæcology, University of Leeds.

DERRICK MELVILLE DUNLOP, B.A. Oxon., M.D., Edin., F.R.C.P., F.R.C.P.E.
Professor of therapeutics and clinical medicine, University of Edinburgh.

EDWARD FORD, O.B.E., M.D. Melb., F.R.C.P., F.R.A.C.P.
Director of the School of Public Health and Tropical Medicine, Commonwealth Department of Health, University of Sydney.

WILLIAM WALLACE STEWART JOHNSTON, C.B.E., D.S.O., M.C., E.D., M.D. Melb., F.R.A.C.P.
Consulting physician, Royal Melbourne Hospital; for services to postgraduate education.

C.B. (Military)

Surgeon Rear-Admiral DOUGLAS MURDO BEATON, O.B.E., L.R.C.P.E., Q.H.P.

Major-General FRANK MCLEAN RICHARDSON, D.S.O., O.B.E., M.D. Edin., Q.H.S.

Major-General THOMAS FREDERICK MACKIE WOODS, O.B.E., M.D. Dubl., Q.H.P.

C.M.G.

JOHN CAIRNEY, M.D., F.R.A.C.S.
Director-General and Inspector-General of Hospitals in New Zealand.

C.B.E. (Military)

Air Commodore WILLIAM PERCIVALE STAMM, M.B. Lond., F.R.C.P., Q.H.S., R.A.F.

C.B.E. (Civil)

STANLEY ALSTEAD, M.D. Lpool., F.R.C.P., F.R.C.P.E., F.R.F.P.S.
Regius professor of materia medica and therapeutics, University of Glasgow.

LOUIS ABEL CÉLESTIN, M.C., M.D. Lond.
For public services in Mauritius.

THOMAS FRANK DAVEY, O.B.E., M.D. Manc.
Senior specialist (leprologist), Eastern Region, Nigeria.

GEORGE LIGHTBODY MONTGOMERY, T.D., M.D. Glasg., PH.D., F.R.C.P.E.
Chairman, Scottish Health Services Council; professor of pathology, University of Edinburgh.

TIMOTHY JOSEPH O'LEARY, M.B. N.U.I.
Senior flying doctor in Queensland, Royal Flying Doctor Service of Australia.

ROBERT WILFRED SCARFF, M.B. Lond., F.R.C.S.
Professor of pathology in the University of London at Middlesex Hospital Medical School.

LEONARD ANTHONY PAUL SLINGER, O.B.E., M.B. Cantab.
Director of medical services, British Guiana.

DOROTHY MARY TAYLOR, M.D. Edin., D.P.H.
Senior medical officer, Ministry of Health.

O.B.E. (Military)

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ALFRED BIMBISARA ABAYOMI-COLE, M.B. Durh.
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Lately deputy secretary, Ministry of Health, and deputy director of medical services, Singapore.

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WILLIAM ALEXANDER CRAMOND, M.D. Aberd.
Physician-superintendent, Woodilee Mental Hospital, Lenzie.

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JEAN ARTHUR GEMMELL, M.B. Edin.
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JOHN ALEXANDER MCVICKER, M.B. Belf.
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ELIZABETH THEODORA MESS, M.B. Lond., F.R.C.S.E.
For public services in the Northern Region, Nigeria.

ALBERTO MARIA RODRIGUES, M.B.E., E.D., M.B. Hong Kong.
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HUGH BRYSON CALWELL WALLACE, M.D. Belf.
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MAURICE HOLLAND WEBSTER, M.B. Aberd.
Director of medical services, Northern Rhodesia; for his work in providing a health service during the construction of the Kariba Dam.
BASIL DUDLEY WHITWORTH, M.B. Camb.
Director of medical services, Swaziland.

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Major DOUGLAS STUART PATON, M.B. Brist., R.A.M.C.

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FRANCES MARY HANCOX.
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WILLIAM ALFRED CONRAD HORTOR, M.R.C.S.
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ADAM SOLTYSIK, M.D. Lwow.
Surgeon specialist, Grenada, Windward Islands.
HENRY THOMPSON STRUDWICK.
Medical officer, Jamaica.

Occasional Book

GÖDEL'S PROOF

IN these days of automation, mechanical translation, and computer-made election forecasts we find mathematics everywhere pervading daily life. We are almost approaching the point where it will be the man who fears mathematics, rather than the absent-minded mathematician, who is unfitted to deal with his environment. It is therefore consoling to hear of a mathematician who can prove that the foundations of the forbidding edifice of reason erected by men such as Bertrand Russell are little more secure than those supporting the ramshackle huts of commonsense which most of us inhabit.

Two American mathematicians, Ernest Nagel and James R. Newman,[1] have lately set out to bring before a wider public the Incompleteness Theorem in which Gödel shows that mathematics contains an inevitable loophole, which may be looked upon either as a fatal defect or else as a vital element of flexibility which saves it from ultimate sterility, depending on the point of view.

Kurt Gödel was born a Czech in 1906 and showed the usual early interest in mathematics. In 1924 he moved to Vienna, there reaching a post equivalent to that of assistant professor in 1933. By then his interests included the philosophical implications of mathematics and it was in 1932 that he made his most individual contribution, by proving, in his own phrase, the "inexhaustibility" of mathematics and publishing his theorem. In 1938 he emigrated to America to work at the Institute of Advanced Studies in Princeton, where he came under Einstein's influence and much of his later work has been concerned with relativity. In 1951 he was co-recipient of an Einstein award.

The proof of his theorem requires the use of a code according to which every possible mathematical statement, argument, symbol, or proof can be translated into terms of a new language. A translation of this kind is loosely similar to translating (say) English into French; but just as a mathematical language or "calculus" is more exact and unambiguous than any ordinary verbal language, so also a mathematical translation or "mapping" is more rigorous and formal than an ordinary linguistic translation.

We may describe a Gödel mapping as a coding procedure capable of converting a page of mathematical argument into a sequence of entirely numerical formulæ. For example, the identity $0=0$ becomes the Gödel Number $2^6.3^5.5^6$ (i.e., 243,000,000) according to the rules of the procedure, and any other sequence of basic mathematical-logical symbols can similarly be represented by a unique Gödel Number. Any Gödel Number can be broken down into its factors in order to arrive at the original mathematical-logical sequence which it represents and as a result of the rigid correspondence between the two parallel languages, the arithmetical relationships existing between different Gödel Numbers stand for relationships between the equivalent statements in ordinary mathematical logic. In other words, statements about Gödel Numbers are statements about mathematical logic (as distinct from statements *within*, or expressed in, mathematical logic). Furthermore the coding-rules devised by Gödel are such that the ordinary laws of arithmetic apply to Gödel Numbers—they may be multiplied, divided, factorised, and so on, as if they were ordinary numbers with no special meaning. It follows not only that arithmetical manipulations of Gödel Numbers are possible and that they are logical statements about logic, but also that the logic in which these statements are made is similar to the logic about which they are made.

When a language (composed of words or symbols of any other kind) is used in order to discuss some other language, such discussions are said to be carried on in a "meta-language". Statements about mathematical logic are therefore called "metamathematical", no matter what terms they are couched in, because mathematical logic constitutes a language; and metamathematical assertions, as we have seen, can be expressed as more or less simple calculations with Gödel Numbers. Since the rules of these calculations are identical with the rules of the original mathematical calculus under discussion, it is clear that in this case the rigour of the meta-language is no greater and no less than that of mathematics itself.

Now it is obvious that mathematics cannot possibly be wholly translatable into another set of symbols (such as the Gödel Numbers) until it is itself expressible in a finite number of symbols. One cannot make a strict translation from French into English of ideas which a Frenchman cannot accurately express in French. The attempt to make mathematics formally and fully expressible has been undertaken by various authors, Bertrand Russell among them, and it is what mathematicians mean by the axiomatic method.

The axioms are the basic unproved assumptions of the system. They are expressed in symbolic form as a set of statements and the symbols are of two types—variables and connecting-signs. The meaning of the axioms resides in the fact that the variables are only allowed to be connected in strictly specified ways—the axioms are in fact the exposition of the ways in which the variables and connecting-signs may be combined, reduced to the simplest terms. In addition to the axioms other "formulæ" can be made up from the same symbols. Formulæ are the formal symbolic equivalent of sentences in ordinary language and the progression from one step of an argument to the next depends on altering the first formula (or sentence) into the next, or combining two formulæ already derived, to produce a third. Strict rules define the permissible ways of making these combinations and substitutions.

A little thought will show that the axioms and the transformation rules together make up the arbitrarily established rational basis of the entire system and are, in short, its "dogma". The symbols serve only as tokens to be manipulated in obedience to the restrictions of this dogma. The axioms of a formal system must all be tautologous—that is to say that the structure of these statements is such that they remain valid irrespective of their content. For example, the algebraic identity $(a+b)(a-b)=a^2-b^2$ is a tautology and it can be verified by substituting for "a" and "b" any numbers

1. Nagel, E., Newman, J. R. Gödel's Proof. London: Routledge & Kegan Paul. 1959. Pp. 112. 12*s*. 6*d*.

we choose. In the same way, the logical axiom: $(pVq) \supset (qVp)$ is tautologous and conveys the same logical attitude about alternative possibilities, whatever phrases or sentences may be substituted for p and q. Furthermore, the transformation rules are such that every formula derived from the axioms by their application must also be a tautology; such formulæ are called theorems. On the other hand, it must also be possible to combine the symbols of the system in such a way that a formula results which is not tautologous, is not derivable from the axioms via the rules, and is therefore not a theorem. Oddly enough at first sight, this last is a necessary condition if the axiomatic system is to be consistent, for the following reason.

By " consistency " is meant that the dogma of the system is such that it is impossible to derive from it both a proposition and its formal contradiction; this is obviously an indispensable condition of rational thought. It can be shown that if both the proposition and its negation can be derived in a single instance, the same can be done for all propositions; therefore, any proposition whatever can be proved and the system is valueless. Conversely, however, if it can be shown by metamathematical argument that there is a single proposition which cannot be proved, it follows that the system is consistent and rational. To prove a system consistent, all that is needed is to discover a single formula which can be shown *not* to be demonstrable from the axioms via the rules and is therefore not a theorem. To prove in addition that a formalised system is *complete* requires a metamathematical demonstration that every true statement expressible in terms of the symbols of the system must also be capable of step-by-step derivation from the axioms.

What Gödel did was to construct the Gödel Number corresponding to a certain formula, this formula being expressed in what purported to be a complete and consistent axiomatic calculus. He also constructed the Number for the negation of this formula. Clearly, one or the other of these numbers must represent a true statement. Now, the formula in question was the meta-mathematical statement that *the formula itself could not be derived* from the axioms via the rules. Thus, either the formula (and the statement) are true, in which case the formula cannot be proved; or else the negation of the formula must be true, in which event the statement must be false and the formula therefore demonstrable although false. Consequently mathematics must either be incomplete or inconsistent, for (when strictly coded into Gödel's meta-language) it permits of the construction of this paradoxical formula.

By similar methods Gödel showed that it was possible to construct a Gödel Number corresponding to the assertion " The calculus is consistent "—i.e., " There is at least one formula in the calculus which is not demonstrable "—and then to show that this assertion was not itself demonstrable by the arithmetical manipulation of Gödel Numbers. The importance of this proof is that arithmetical reasoning is shown to be insufficiently powerful to demonstrate its own consistency; the possibility is, however, left open that the consistency of mathematics might be demonstrable in terms of a non-mathematical meta-language.

There is an interesting psychological application of the second of these two proofs. When the attempt is made to prove the absolute consistency of a formal calculus in terms of a meta-language which obeys the same dogma as the calculus itself, the situation is similar to that of a man who attempts to calibrate one instrument, such as a ruler, against another from the same factory. The best that can be hoped is that the measurements made by the two instruments will lend each other support; for, when they disagree, neither can claim the final authority. If we accept that human reason is incapable of achieving a watertight proof of its own rationality, even in the strict language of formal logic, the same must apply still more forcibly to reasoning carried on in the far less precise and stable language which we ordinarily use, unless we relinquish the hypercritical standards of absolute proof which logicians demand. The critical evaluation of one's own reasoning, in short, is probably quite as fallible as the reasoning itself; and " second thoughts " no more reliable than " first impressions ".

If it is correct to argue from the particular case of mathematics in this way, then when a man analyses a possible flaw in his own thinking, he is indulging in what might be called " meta-thinking " and the result is liable to be a deadlock unless either he is prepared to be content with something less than certainty, or he is capable of greater rigour in his meta-thinking than in his suspect first thoughts. We know that this type of deadlock can occur and may reach pathological dimensions; the perfectionist is very prone to lapse into obsessional doubt, to demand absolute certainty and to ruminate ceaselessly on one topic or another. It is perhaps also relevant that one symptom of the severe anxiety to which obsessionalism can lead is the fear that reason may be completely lost. The analogy with " inconsistency " needs no underlining.

From a therapeutic standpoint these considerations suggest that such people may be helped, in general, by whatever gives them the confidence to accept a degree of uncertainty—whether this agent be a pharmacological euphoriant or some kind of reassuring relationship. Indeed, we do find that obsessional people tend to seek a father-figure. Another approach should theoretically be the introduction of a fresh meta-language, capable of greater rigour than either the first thoughts or the critical second thoughts of the patient; in other words, someone who will do his meta-thinking for him. This interlocutor would have to be of higher intellectual discrimination than the patient and free from the particular preoccupation which besets him; he would then be in a position to redefine the problem and to throw his weight on one side or the other.

In practice the necessary " third language " is often provided by an established source of formal dogma covering the main area of conflict, whether it be religion, politics, sex, or some narrower topic. A dogma relieves the victim of any need to decide and may liberate his mind for other pursuits; but for this recourse to be available to the patient the source of dogma must be acceptable. It may be that the occasional effectiveness of analytical psychotherapy in relieving what are, in effect, deeply buried obsessional pre-occupations (" conflicts ") depends upon a combination of two simultaneous processes—on the one hand the gradual eliciting of material and the analytical breakdown of the patient's problems to a few central issues; and on the other, the cultivation of a transference relationship which establishes the analyst as an acceptable source of dogma on these issues.

The psychological analogy with Gödel's work provides a crumb of comfort for those who occasionally doubt their own sanity. It will be remembered that in the first of his proofs, the alternative to mathematics being irrational and inconsistent was that it must be incomplete. Gödel himself regarded this second alternative as meaning that mathematics was an inexhaustible field for empirical discovery; and it is consoling, surely, to feel that one can interpret one's state of mind at such times either as insanity or as intellectual fecundity.

In England Now

A Running Commentary by Peripatetic Correspondents

As I approached the group of five-year-olds, I could see that they were in a state of anxiety and excitement. One of them, Samuel, was near to tears. At their side Samuel's large dog was happily eating my sandwich lunch. "Quickly, quickly," cried a little girl, "the dog is eating your sandwiches." And Samuel added his plea, "Hurry up, Mister; white bread is bad for him."

* * *

I have lately received a number of inquiries which show that in these days of crowded resorts and high fares the hospital holiday is becoming increasingly popular. Many people, I know, look with disfavour on surgical operations, though in my opinion this is generally based either on misconceptions or on deliberate misrepresentation by selfish addicts who fear to see their own pet preserves invaded. I myself have always found a visit to one of our justly famous hospitals a very pleasant change.

Last year I hesitated for some time between a festival of modern music, an undoubtedly attractive tour organised by a botanic garden expert, and one of the big peace marches; but recalling the delights of previous experiments in this somewhat lesser-known field—the nurses, the flowers, the grapes, the hours of leisurely reading—I found myself once again unable to resist the call of the clinic.

Here let me sound a note of warning. Just to decide upon any operation, without paying due attention to the enchanting alternatives offered, is equivalent to saying "I'll go to Italy" instead of "I'll go to Cannobio or Torri del Benaco". And I am sure I shall hurt no surgeon's feelings—and it is my considered opinion that no body of men has done more for the tired business man than our surgeons—when I remind readers that, just as there are hospitals and hospitals, what may be suitable for one man may prove disappointing to another. Indeed, there are as many fascinating facets to the relinquishment of superfluous parts of the human body as there are lakes in Italy and Switzerland, or forms of Roman or Florentine architecture. I heard, for example, of a chartered accountant who, wanting just a short break from an arduous but lucrative practice, made the mistake of choosing an incision instead of an excision. His disappointment was intense, and he returned to his office feeling little better for the change. True, the holiday was not a total loss: there was the initial anæsthetic—that delightful moment equivalent to the first trembling of the boat beneath one's feet or the sight of the trees falling away as the plane takes off—but the exhilaration of awakening from deep sleep to find that yet another unwanted oddment of the body had been sloughed off was lacking.

The wise man will select his hospital as carefully as his operation, and here let me say that it is no longer necessary to confine oneself to the better-known resorts. The large and fashionable establishments such as Guy's and Barts naturally offer a wider range of exciting and even novel possibilities, and are, of course, famous for their varied choice of anæsthetics, but many smaller and less-known hospitals cater for the discerning visitor who prefers to go somewhere more off the beaten track, and at a price to suit even the slenderest purse. I know of one small and unpretentious establishment within twenty miles of London which will do an all-in appendectomy for very little more than the cost of a visit to Glyndebourne.

Few who have not experienced this type of rest cure can realise to the full the amenities of hospital life. At what hotel, for example, are *all* meals served in the bedroom without extra charge? At what hotel will the chambermaids uncomplainingly make your bed while you are still lying in it? At what hotel will that same bed be moved in fine weather on to an airy balcony, or two creamy arms raise you carefully on your pillow when you wish to read and lower you as tenderly back when you wish to sleep?

I fear I may be taken to task if I fail to point out that many hospitals are as yet unlicensed, though an occasional glass of brandy can, I am told, be obtained by those who know the ropes. In my opinion, however, this point is of less importance than might at first appear. I have already referred to the variety of anæsthetics available to guests in most of our hospitals, and a wide choice of out-of-the-way beverages is to be found in the cellars of the more select houses; and I have yet to meet the connoisseur of fine drinking who, once he has discovered the fascinating bouquet and colour of some of the really great prophylactics, will willingly revert to his former tastes.

One last word of warning. Though hospital holidays are not yet fully commercialised, more and more people possessed of the pioneering spirit are becoming aware of their possibilities, so that already a certain amount of advance organisation is necessary. Inquiries can be addressed, through your own local agent, to any reputable specialist.

* * *

When I start to do a barium meal I usually like to get some grasp of the patient's complaint with the help of a few opening questions about gastrointestinal symptoms. The replies are varied, often irrelevant, and often at variance with the history which has been elicited by another consultant in the outpatient department, though not necessarily on that account any less accurate. Perhaps the most unkind reply, however, was "I have had everything wrong that my doctor can think of, so he sent me along here for an X-ray".

* * *

It is all very well to bemoan the pædiatrician's burden at Christmas, but has anyone given a thought to the burden of the psychiatrist in a mental hospital?

It was the Medical Superintendent's idea. "All part of the open-ward policy," he explained. "Father Christmas means freedom for millions. A visit from him, more than anything else, will show our chronic patients that they're free to come and go as they please. And you, Smith," he paused and looked at me, "will be Father Christmas".

On the day I was dressed up, given a large gin and, to the accompaniment of raucous cheers from people I had hitherto regarded as friends, started my round. At the first ward the patients were all gathered in the entrance hall. None of them took the slightest notice of me, despite the nurses' attempts to stir up excitement. I left quickly for the next ward, my spirits rising as I calculated that I ought to be back in the mess in a quarter of an hour. This shows how fatal it is to make predictions, for in the next ward I met someone who really was Father Christmas. He was seething with rage at the idea of being impersonated. He told me that he was the one and only Father Christmas and that I was almost everything under the sun except Father Christmas. I was so alarmed that I stepped backwards and, tripping over my gown, fell on my back. For one dreadful moment I lay helpless. Then I had one of those rare moments of inspiration. "Your Majesty," I babbled from beneath my beard, "I am not Father Christmas. In fact I have come especially to find and escort you round the hospital. The reindeer have been delayed, but we can walk..." It was four hours later before I got back to the mess.

Father Christmas is a changed man and the Medical Superintendent hopes to discharge him home shortly. As for me, I'm thinking of emigrating to one of the less progressive countries before next Christmas.

* * *

The other day I used the word "carminative" and was promptly asked by a member of my family whether I was referring to one of the B.M.C. new baby cars.

* * *

OATS AND CIRCUSES

Mokerleatotes
Givvimum inbag
Scotterleatotes
Givvimum indish
Anybody mustavvizotes
Givvussor larotes
Wile dotes anantidotes
Forplentiotes
We votes.

Letters to the Editor

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—Having for some years made a practice of carefully observing infantile cavernous hæmangiomas, and having rarely undertaken any early treatment for these lesions during this period, I am surprised at Mr. Denis Browne's strictures on Dr. Simpson's article (Dec. 12). It is my practice to explain to the mother the facts about the natural resolution of the majority of cavernous lesions; if necessary to show her photographs of cases in which this has occurred, and to ask for her cooperation in regular observation of the baby. In my experience the mothers are happy to follow this course, and on only one occasion has a baby subsequently been taken elsewhere (in this case to a radiotherapist who treated the lesion). I have found that, despite early enlargement of some of these hæmangiomas during the first six months, the ultimate results have generally been most satisfactory. Residual lesions can be excised if necessary but it is unusual for the final condition to warrant this.

Dr. Jones states that statistics can be misleading and that large numbers must be studied. It is a common fallacy that "large numbers" add to the validity of observations whereas the careful observation of small numbers of strictly comparable cases is often far more rewarding. The figures quoted by Dr. Jones are certainly rather confusing. Thus, at the Presbyterian Center, New York, it is stated that 135 out of 584 patients with cavernous hæmangiomas were untreated, and Dr. Jones seeks to compare these with Dr. Simpson's 170 lesions of which 140 were untreated. I would submit that it is unwise to attempt to compare the two series. However, if one is seeking information about the natural history, Dr. Simpson's series (in which 82% of lesions were not treated) should be more informative than the American series in which only 23% of patients were untreated. Dr. Jones includes reference to 329 patients with hæmangioma simplex in the American series, but Dr. Simpson's paper was not concerned with this type of case.

Dr. Jones goes on to refer to 814 out of 1752 "angiomas" (were these all cavernous?) which received X-ray therapy in Sussex and Kent. He states the criterion of recovery but gives no information about the results achieved, or when the improvement occurred. It is implied that a number of cases had repeated treatment and it is plain that almost 25% were still being treated after a five-year period. Dr. Jones also states that only 20% cleaned in the first year. I must confess that I find it impossible to gain any precise idea of the Kent and Sussex results referred to by Dr. Jones though I gather that he regards the cosmetic result as better in the treated cases.

I have read Dr. Simpson's paper with care and, as a surgeon, I find little with which I disagree. In his discussion he makes it perfectly plain that residual lesions can be better treated at a later date, but his brief summary gives a slightly misleading impression of his views in that it baldly concludes "no treatment is necessary".

London, W.1. REGINALD S. MURLEY.

LEAF PROTEIN AS HUMAN FOOD

SIR,—It would be superfluous to say that Mr. Pirie's proposals for the use of leaf protein as human food (Nov. 28) are highly commendable and deserve success but there are blemishes in his argument that should be removed.

He stated that "it is likely that a deficiency of any aminoacid in one protein (in leaf) will be compensated for by the other proteins, so that there will be no extensive deficiencies or excesses in the mixture". Likely perhaps, but, unfortunately, not true.

Cabbage protein [1] contains less than 50% of the isoleucine, leucine, S aminoacids (i.e., methionine + cystine), phenylalanine, and valine of egg protein, which can be regarded as the standard. Kale contains less than 50% of the isoleucine, lysine, and S aminoacids; mustard greens less than 50% of the threonine, isoleucine, leucine, S aminoacids, and phenylalanine; sprouts less than 50% of the isoleucine and leucine of the egg standard. These analyses are supported by biological estimations on cabbage protein [2] and two fractions of grass protein.[3]

The primary requirement of a protein supplement for human feeding is a high content of methionine and cystine as most human diets are limited by this pair of aminoacids.[4] Leaf proteins make no major contribution to this demand. The isolated proteins of lucerne [5] contain 50% of the methionine + cystine of egg, 60–70% clover, 55% groundnut leaves, 50% barley grass protein.

The experiment on pigs quoted by Mr. Pirie, showing that leaf protein was as good as fish meal, was supplementation of a cereal ration in which lysine, not methionine, was limiting. Further, the level of protein fed was too high to reveal possible differences between leaf protein and the fish-meal control. (Moreover, fish meals can range from poor to good as proteins go.)

These limitations are set out not to abolish but merely to reduce the height of the hopes set on leaf protein.

This said, there remains the enormous problem of presentation. Mr. Pirie speaks of British prejudice to the green colour, but prejudices are worldwide and difficult to overcome. In Guatemala the protein intake has been substantially increased in an acceptable way by adding cottonseed-maize to the local gruel. This procedure is not acceptable across the border, because the supplement imparts a slight colour to the food. This would suggest that no efforts should be wasted in offering leaf protein to verdophobes but only to such areas where the colour is considered advantageous.

What is needed is a good cook/chemist/home-economist to produce an edible finished product that suits local custom and thus becomes acceptable.

Bovril, Limited,
London, E.C.1. A. E. BENDER.

SIR,—Mr. Pirie's reply (Dec. 26) to the letters of Dr. Cicely Williams and Mr. Allen deals effectively with their criticism, and clarifies a number of the details mentioned in his original article. The problem of getting enough food is a desperately serious one to millions of people, and it is encouraging to see basic research directed towards its solution. There are a couple of points which have been raised in the present discussion which seem to me to merit amplification.

The first is the question of the nutritional value of leaf protein. Mr. Pirie states that for pigs, chickens, and rats the protein extracted (from English leaves) is as good as, or a little better than, fish meal, "though not as good as the pre-eminent proteins—casein and egg albumin". If this is found also to be true for human children and tropical leaves, it will be good news for those areas where there is a deficiency of total protein

1. Amino-acid Content of Foods. Home Economics Research Report no. 4, U.S. Department of Agriculture.
2. Bender, A. E., Miller, D. S. Unpublished data.
3. Davies, M., Evans, W. C., Parr, W. H. *Biochem. J.* 1952, **52**, xxiii.
4. Miller, D. S., Dema, I. S. *Proc. Nutr. Soc.* 1958, **17**, i.
5. Proteins in Foods. Indian Council of Medical Research, 1958.

in the diet. However, there are many areas where the dietary intake of protein appears to be adequate but signs of protein deficiency still abound; and it is found that the protein is almost exclusively of vegetable origin. In Uganda, for instance, there is an impressive amount of kwashiorkor, and of the milder form manifested by retardation in growth; but recent experience with distribution of skim milk powder [1] showed that even those children who received a relatively small amount (well below the amount currently recommended by UNICEF) showed a substantial improvement in weight gain. The proceedings of the Third Inter-African Conference on Nutrition [2] bear witness to the need for further investigation of the nutritional status of groups consuming different proportions of foods of animal and vegetable origin, and this was emphasised in the recommendations of the conference. In her admiration for Samuel Smiles, Dr. Cicely Williams may be contemptuous of "the teaching propounded by foreigners, who have spent most of their time concentrating on the virtues of skimmed milk"; but virtues cannot be lightly ignored, even if propounded by foreigners. Self-sufficiency, particularly in the production of foodstuffs, may seem elementary good sense; but I have the impression that economists are all in favour of trade, and there appears to be plenty of scope for trade in skim milk powder—if only the powers-that-be would develop it.

The other point, a small one, springs from Mr. Pirie's observation that there is room for improvement in the varieties of vegetables grown in the tropics. Indeed there is; and for passing on the knowledge to local farmers. At present, economic interests being what they are, tropical plant breeders are occupied almost exclusively with improving cash crops—cocoa, cotton, coffee, &c.—and with making these available to farmers. Even where better varieties of food crops have been bred (as with maize at the Cotton Research Station in Uganda) no effort is made to encourage their use by farmers. Here again there is scope for action by the powers-that-be.

The National Hospital,
Queen Square, London, W.C.1. JOHN MCFIE.

SIR,—Are not Mr. Pirie (Dec. 26) and Mr. Allen (Dec. 12) both partially correct? Of the nutritive value of leaf-protein there would appear to be no doubt, but as a processed food for human consumption would there not be many difficulties?

The essential reason for malnutrition, certainly as one saw it in the 1930s in Southern Nigeria, was poverty. The same period coincided with the effects of a world economic slump which led to a prolonged and catastrophic fall in local produce prices.

While recognising that certain basic dietaries in parts of Nigeria are much more vulnerable than others, one must appreciate that millions of Africans live a normal healthy life, supplementing their own dietary. Any new food concentrate would have to have a very special appeal and be available to those most needing it without extra cost.

Actually the introduction of what is essentially a protein supplement would not be new to Nigeria. I understand that attempts are now being made to popularise 'Food Yeast.' My own experience was with 'Marmite', and the demand for it later became so great as to far exceed its therapeutic use. Its success depended on: (1) as a therapeutic agent it was dispensed free; (2) it had a visible effect on what was then a very prevalent condition; (3) its palatability appealed to those otherwise dependent on a predominantly vegetarian diet; and (4) it did not offend dietary custom or habit.

I also used a large amount of dried brewer's yeast. Though effective therapeutically, its taste made it unpopular.

I doubt whether a protein leaf concentrate would achieve any direct objective. On the other hand, provided costs permit, it could be supplied to animals and thereby be an indirect source of food.

Parkstone, Dorset. D. FITZGERALD MOORE.

1. Welbourn, H. F. *Lancet*, 1959, i, 1248.
2. Proceedings of 3rd C.C.T.A. Inter-African Conference on Nutrition, Angola, 1956.

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—Blind gastrectomy has saved and will save many patients who would otherwise die of hæmorrhage. We must stop the bleeding without exhausting the patient's reserves. By all means let us try any promising method, such as that quoted by Mr. Downie (Dec. 12). But once it is clear that operation is necessary a determined policy must be pursued. This means rapid replacement of blood, and operation within two hours of the decision to operate.

When the abdomen has been opened the following rules will help young surgeons who have to do the bulk of this work.

(1) Exclude portal hypertension.

(2) Rapidly examine the upper jejunum for contained blood. If present, bleeding is active and there is need for haste. If absent, examine the ileum. Blood within often means that bleeding from the upper alimentary tract has temporarily ceased and there is more time for search.

(3) Inspect and palpate the proximal duodenum and the whole of the stomach. The left hand is the more useful. Open the lesser sac with the forefinger and middle fingers above the stomach and palpate the back of the stomach. An irregular fatty patch with irregular vessels near the lesser curvature on either surface indicates an ulcer. If the stomach contains much blood, open it at once. Remove clots manually and fluid with the sucker. (Twice in one week I found large holes in the splenic artery from ulceration on the back wall of the stomach, far to the left.)

(4) If no obvious source of bleeding is found re-examine more thoroughly the whole of the small bowel, looking especially for such lesions as the hæmangiomata described by Mr. Lytton (Dec. 26) and Mr. Read (Jan. 2), or an ulcer in a diverticulum.

(5) If no bleeding point or ulcer has been found do not make further search in the stomach but do a two-thirds Polya gastrectomy. In the course of this the bleeding point may become obvious, as for instance a small ulcer on the postero-inner wall of the duodenum. The crater may be seen in the open duodenal stump, or the artery (usually a short branch of the anterior pancreatico-duodenal) may be seen spurting while the duodenum is being cleared.

After operation examine the excised stomach, slitting up the greater curvature. The bleeding point may sometimes be found on holding the specimen up against the light. Mark any suspected area with a black silk stitch as a guide to the pathologist.

With such a policy, a few stomachs will be needlessly sacrificed but many lives will be saved.

Edgbaston,
Birmingham. FAUSET WELSH.

SIR,—The discussion provoked by the two articles on hæmatemesis (Dec. 5) raises the important issue of selection of patients for operative arrest of the bleeding. There is little doubt that a policy of selective surgery is effective in lowering the mortality from hæmorrhage provided that an early decision is reached in suitable cases. Early identification of the lesion responsible for bleeding is of great importance in this connection so that patients with recurrent hæmorrhage from chronic peptic ulcers can be operated upon without delay.

At the Central Middlesex Hospital we have attempted to meet the need of early ætiological diagnosis by a combined procedure of immediate gastric aspiration (for pH analysis), followed the morning after admission by gastroscopy and shortly thereafter by barium-meal examination done on the ward using a portable X-ray apparatus. Of the last 150 admissions for hæmatemesis correct diagnosis has been achieved in 80% by this method, usually within 36 hours of admission. The possession of information of diagnostic value as to the cause of

illness in circumstances of recurrent bleeding greatly assists the often difficult choice between operative and conservative treatment. Indeed, in the last week during a surge of peptic activity in north-west London, 6 patients have undergone emergency gastrectomy for bleeding in this hospital, and in all but 1 patient, whose restlessness prohibited investigation, the decision to operate was undertaken with foreknowledge of the responsible lesion. 4 of these patients were bleeding from chronic gastric ulcers, a group in whom surgical treatment is particularly indicated.

The importance of reaching an early decision between surgical and medical treatment of bleeding peptic ulcer cannot be overemphasised, for rapid deterioration despite apparently adequate replacement of blood by transfusion is common and delay in seeking surgical aid too often fatal. It is our experience that the procedure of early investigation is both informative and harmless and is an important factor in the successful management of patients bleeding from an unknown lesion in the gastrointestinal tract.

Though full investigation by pH analysis, gastroscopy, and early X-ray examination may be impracticable in most hospitals, we have found that ward barium-meal examination using the portable X-ray machine gives diagnostic information in more than three-quarters of patients admitted after hæmatemesis. This simple radiological procedure is well within the scope of a general hospital. The detailed technique will shortly be published.

Department of Gastroenterology,
Central Middlesex Hospital,
London, N.W.10. G. N. CHANDLER.

POSTCOITAL EXAMINATION OF SEMEN

SIR,—For the past twelve years I have, with few exceptions, referred all husbands of my infertile couples to Dr. Davidson (Jan. 2)—several hundred of his 12,000 cases. From my personal experience I can say that Dr. Davidson's direct semen examination has "saved many women a great deal of unnecessary investigation, discomfort and eventual frustration". The majority of subfertile men can be improved.

I can endorse everything Dr. Davidson has said in his letter.

Croydon. ARTHUR CLIFT.

DENTISTS AND ANCILLARIES

SIR,—I must point out that Mr. Markham (Dec. 5) failed to stress the fact that insufficiently trained persons will be practising on the youth of this country if dental ancillaries are in being.

Your remarks about the apparently unattractive nature of the work of a dentist seem contrary to the fact that some hundreds of applicants all over the country are being turned away annually by the dental schools. In the House of Commons, Mr. Walker-Smith admitted: "As a matter of fact there is no shortage of recruits to the dental profession at the present time." He did not think inducement grants were needed. "It is really a matter of accommodation, and we are getting on as fast as possible."

Surely the public, and in particular the children, are entitled to dental treatment by fully trained and qualified dental surgeons. 38 years after the 1921 Act we still see the results of unskilled treatment, and while the dental surgeon of today is doing his best in his overcrowded day, the Government, apparently with your approval, is going back half a century.

Does the medical profession not realise that this dilution of the dental profession is not in the interest of either the profession or the public; it is Government chicanery to attain cheap dentistry, and the shortage of dentists is being put to good use.

The medical profession is being abused because of possible overcrowding. Were there a shortage of doctors, I wonder what type of ancillary would be introduced.

Instead of quarrelling about the fact that young dentists by hard work and long hours can earn professional remuneration, while young doctors are being exploited, as complementary professions each should be understanding of and sympathetic to the other and work together for their mutual benefit.

If the ancillary experiment is a success and I have no doubt that it will be, we shall see the beginning of the end of dentistry as a profession and a distinct fall in the standard of dental treatment. If the new ancillary training hospital at New Cross was to be used for the training of dental surgeons, and if the project Mr. Walker-Smith has in hand of admitting 900 dental students per annum was speeded up, there would soon be no shortage of dentists.

London, N.W.7. M. CHALMERS.

CLASSIFICATION OF CHRONIC BRONCHITIS

SIR,—Your annotation of Dec. 19 rightly draws attention to the necessity for an agreed nomenclature in regard to the clinical condition which, in this country, is traditionally called "chronic bronchitis". At present we are largely ignorant of the natural history and causes of this disease, so that any classification to be generally acceptable must be simple and based on easily distinguishable clinical features. Fletcher's excellent classification,[1] to which you refer, points the way, but is too elaborate for widespread use. If kept to its three broad categories, it is a useful basis from which further subdivisions may be made.

The first type which Fletcher has called "simple chronic bronchitis" would surely be better termed "bronchorrhœa". This avoids the suggestion inherent in the word "bronchitis" that the process is inflammatory, and so far as I can ascertain from medical dictionaries, simply means "an excessive discharge of mucus from the air passages of the lungs", and has no other connotation.

Fletcher postulates infection as the dominant feature of his second type. It may be only pedantic to argue that mucopurulent sputum, or recurrent chest illness, is not always evidence of infection, but certainly there is a difference between the hearsay evidence of the patient reporting thick yellow phlegm, and the physician actually observing purulent sputum; just as there is a difference in the readiness of different patients to admit to "recurrent chest illness". Nevertheless, it is this second stage of bronchitic disease which is likely to be the most important clinically during the next few years, and an acceptable classification could usefully postulate the objective observation of the patient's purulent sputum.

Until recently, any definition of ventilatory impairment has been difficult because subjective appraisal differs widely. Fortunately, Wright's peak expiratory flow-meter now affords a means of evaluation of ventilatory capacity which can be measured easily and quickly in any hospital outpatient department, and a peak expiratory flow-rate of, say, less than 300 litres per minute could be arbitrarily accepted as a definition of moderate ventilatory impairment in a bronchitic subject.

The three stages of bronchitic disease might therefore be (1) bronchorrhœa; (2) recurrent infective bronchitis; (3) recurrent bronchitis with ventilatory impairment. All these can, of course, be subdivided.

If some responsible body closely associated with research in this field arbitrarily ventured to postulate its definitions, it might be a considerable encouragement to individual research-workers to publish their findings in terms of such definitions which would facilitate the comparison of published work.

Bournemouth Chest Clinic,
Westbourne, Bournemouth. W. H. TATTERSALL.

1. *Amer. Rev. resp. Dis.* 1959, **85**, 483.

PYELOGRAPHY IN URINARY INFECTION

SIR,—"Pyelography not yet justified . . ." This statement in Dr. James' article (Dec. 5) prompts me to ask again: when is pyelography justified in renal-tract infections? While R.M.O. at Salisbury General Infirmary recently, I included intravenous pyelography as a routine investigation in all acute renal-tract infections amongst the nursing staff. The total number of such cases was quite low but, to my surprise, three pyelograms revealed evidence suggestive of obstruction: in two there was persistent unilateral ureteric kinking and in a third a double ureter was shown on one side. As these were all first infections in otherwise healthy young girls surgical intervention was not sought. I am still wondering whether this was the correct attitude or not.

There is a wealth [1 2] of experimental and presumptive clinical evidence showing a correlation between obstruction and renal-tract infection. Of the possible permanent sequelæ to such infection we are only too well aware. That obstruction was a possible factor in the pathophysiology of these cases I had little doubt. Yet I am sure most surgeons would be loathe to intervene in the absence of more positive evidence, such as persistent or recurring infections, or calyceal distortion. Logic teaches that this is obviously too late and that many cases of occult persistent infection will be missed. Nevertheless until we are prepared to investigate and treat actively all cases of "minor" anatomical disturbance I see little point in routine pyelography. I wonder does Dr. James think likewise?

St. Vincent's Hospital, Dublin. JAMES G. DEVLIN.

TROPHOBLAST AND ITS TUMOURS

SIR,—If the trophoblast is a homograft, the full implications do not appear to be yet realised. Surely if tolerance to a homograft can be induced in a fœtus or newborn animal, but not an adult animal, by injection of donor cells it is an unjustified extrapolation to suggest that a similar mechanism occurs in the human adult pregnant female host. This topic is not new; in your columns I pointed out ten years ago [3] in detail the inconsistencies that the present hypothesis leads to and suggested an alternative. The alternative is that the trophoblast is an autograft, at least the syncytial portion of it, and derived from the granulosa cells that cover the ovum when it leaves the follicle.

Unorthodox as this suggestion is it at least makes sense, which the present orthodoxy does not. I suggest that the main function of the syncytium is to protect the fœtus from the homograft reaction of the mother, and perhaps vice versa to protect the mother from the fœtus. Remember that however separate the fœtus may be from the mother the syncytium is as intimately involved in the maternal circulation as any cells can be.

Public Health Offices, Ilford. ISRAEL GORDON
Medical Officer of Health.

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—The article by Dr. Coffey and Professor Jessop (Nov. 28) merits further comment, especially in view of two contradictory reports on this subject. In all likelihood, these reports were not available to Dr. Coffey and Professor Jessop when they completed their study.

1. *Lancet*, 1959, i, 614.
2. *ibid.* p. 1265.
3. Gordon, I. *Lancet*, 1949, i, 807.

Wilson and his co-workers as a result of their investigation [1] concluded that "No significant teratogenic effect of Asian influenza was demonstrated . . ." It is to be noted that the presence or absence of influenza in the patients they studied was confirmed by hæmagglutination—inhibition titre determinations.

Walker and McKee [2] have concluded that "there was no apparent alteration in the number of anomalies in the infants of mothers who had Asian influenza during their pregnancy". In this study serological tests for influenza similar to those employed in Wilson's investigation were also carried out.

On the basis of the findings of Walker and Wilson one might well question the implications of the Dublin study. Moreover, the methodology of selecting patients for inclusion in the study on the basis of self-diagnosis is vulnerable to criticism. This is so, not so much (in this instance of a disease with a high attack-rate) because those replying in the affirmative may not have had the disease, but, as Walker's study points out, because those replying in the negative may very well have had the disease.

Seaside Memorial Hospital of Long Beach, Long Beach, California. GEORGE X. TRIMBLE
Director of Medical Education.

FORMATION OF RENAL CALCULI

SIR,—I was very interested indeed to read your annotation of Oct. 24.

I have been carrying out a small experiment to try to confirm or refute the claim that the administration of salicylates prevents the formation of urinary calculi.

Medo-Chemicals Ltd. have very kindly supplied me with a stock of their 'Salimed' tablets and also some pseudo-salimed tablets, and I have been administering these to an unselected group of patients who have had recurrent urinary calculi, but in whom there is no local predisposing cause to recurrence, such as chronic infection or stasis. This is obviously a very long-term type of investigation and as yet it is not possible to draw any conclusions.

I know that claims have been made in America, both for and against its administration, but I feel that both these investigations were not sufficiently selective or continued for a sufficient length of time to justify the conclusions. I hope in a few years' time that I shall be able to give some results which may help to decide whether there is any value in the administration of salicylates, or salicylate-containing substances, to patients with recurrent calculi.

Hove, Sussex. S. H. C. CLARKE.

ÆTIOLOGY OF LEUKÆMIA

SIR,—The theories discussed in your leading article [3] on the ætiology of leukæmia are intriguing. However, some results of our studies on human leukæmic leukocytes in vitro are in disagreement, not only with the concept of chronic leukæmia as a conditioned neoplasm resulting from deficiency of a blood-borne growth inhibitor but also with the thesis that autonomy of leukæmic cells (i.e., in acute leukæmia) might be specifically indicated by an abnormal chromosomal pattern. We failed to find any chromosomal abnormality in the three cases of *acute* granulocytic leukæmia reported some time ago,[4] and more recently we have found a small, but definite, abnormality, a minute replacing one of the 46 normal chromosomes, in the 2 cases of *chronic* granulocytic leukæmia investigated.[5]

1. Wilson, M. G., Heins, H. L., Imagawa, D. T., Adams, J. M. *J. Amer. med. Ass.* 1959, **171**, 638.
2. Walker, W. M., McKee, A. P. *Obstet. Gynec.* 1959, **13**, 394.
3. *Lancet*, 1959, ii, 447.
4. Nowell, P., Hungerford, D., Brooks, C. *Proc. Amer. Ass. Cancer Res.* 1958, **2**, 331.
5. Nowell, P., Hungerford, D. (to be published).

Further, in studies involving both acute and chronic granulocytic leukæmia and acute monocytic leukæmia, we have been, thus far, unable to show any difference in either mitotic activity or differentiation of leukæmic cells in vitro, whether grown in normal or in leukæmic plasma.[6]

Pathology Department, School of Medicine, University of Pennsylvania, Philadelphia. P. C. NOWELL.

Institute for Cancer Research, Philadelphia. D. A. HUNGERFORD.

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—The problem of inadequate sources of blood for replacement after massive hæmorrhage is probably the main bugbear of surgery in many hospitals overseas. Fortunately, as Mr. Azie points out (Dec. 12), in the patient with ectopic gestation we have adequate blood reserves available—her own.

In this hospital the patient is sent immediately to theatre, and a drip started. Anæsthesia takes no longer than adequate scrubbing by the surgeon, and saves the patient from the added shock of seeing her own blood being, as she thinks, sacrificed.

Through a small nick in the peritoneum a fine "sieve"-ended cannula is inserted into the cavity and the free blood drawn into sterile citrated bottles while adequate exposure is made in the more superficial layers. This decompresses the abdomen and minimises blood wastage. The blood collected is returned to the patient through the drip at maximum speed, the first litre being given in 5 minutes. The subsequent rate is controlled by the patient's condition. The blood-bottle filters seldom show clot, and we have now records of over fifty cases without mishap, and up to 2 litres of peritoneal blood have been given.

Theoretically, this technique is open to objections, but to those of us who serve on the frontiers of medicine the consistently good result justifies its use. We have tried the collecting, whipping, straining, and reinjecting methods and have rejected them in favour of a technique as safe as it is simple. The patient is back in bed within half an hour often apparently little the worse for her experience, except for the loss of her tube.

Finally, Sir, may I express my appreciation of the fact that your highly scientific journal finds space for the description of techniques which, though unnecessary in highly developed countries, may still save many lives in less fortunate areas.

Kwahu Hospital, Mpraeso, Ghana. J. ASHFORD HYDE.

SIR,—I was interested in the recent letters from Mr. Azie (Dec. 12) and Prof. Chassar Moir (Jan. 2) on emergency resuscitation by the use of the patient's own blood removed from the abdomen and think it may be of interest to record an early instance of the use of this method.

In the spring of 1915 at Bethune I saw Capt. John Fraser (later Prof. Sir John Fraser) use blood removed from the abdomen of a man suffering from a gunshot wound, for transfusion after filtration through silk. I do not know whether this was ever recorded elsewhere but at that time, when blood for transfusion was unobtainable, the method was regarded as unique.

Ickleton, Saffron Walden. CLAUDE FRANKAU.

6. Nowell, P. *Exp. cell. Res.* (in the press).

URINARY INFECTION IN THE NEWBORN

SIR,—I am grateful to Dr. Brown (Dec. 19) and Dr. McNicholl (Jan. 2) for their comments on my paper of Dec. 5. I regret that the pus-cell counts were omitted and they are given in the accompanying table.

		Growth of organisms			
		Sterile	Scanty	Moderate	Heavy
No. of cases		4	82	9	5
Pus-cell count	Males	..	141→10 750→20 Others less than 24	10 138→10	27 1000→48,000 1000→ 1150 1000→ 1200
	Females	Less than 33	Less than 40	108→24 261→52 Others less than 32	11

I agree with Dr. Brown that the criteria for diagnosis must be carefully assessed, and for this reason I stressed that the cell-counts in the urine must be repeated in cases of doubt, especially where there is lack of correlation between cell-count and culture. He will also see that a second count is recorded in the chart reproduced in my paper.

I have observed that the incidence of neonatal urinary infection varies from time to time in the same maternity unit even when constant criteria are used for diagnosis, but for this I can give no explanation.

Pus-cell counts in a measured quantity of uncentrifuged urine can be reported with accuracy and results are comparable from any hospital or laboratory, whereas microscopic-field counts must vary according to the size of the drop held by the coverslip.

Stansfeld [1] reported that an average of 1 pus cell per high-power field was approximately equivalent to 250–500 pus cells per c.mm. of uncentrifuged urine. It is therefore evident that this method of urine examination is unsuitable for demonstrating urinary infection in newborn babies.

I am most interested in Dr. McNicholl's report of hæmolytic anæmia associated with renal infection. I have had 2 similar cases, but in each of them the blood-culture for *Escherichia coli* was positive. I have observed no other cases.

London, W.1. URSULA JAMES.

PRISONS

SIR,—Your leader of Dec. 5 rightly applauds the work of the prison service in the face of an increasing prison population, but makes no mention of the appalling physical conditions existing in some prisons today. Improvements in the prisoners' uniform and relaxation of the "silence" rule in workshops can only partially alleviate the problems posed by buildings which are frequently over a hundred years old, inadequately heated, and provided with sanitation barely fit for animals.

An offender is sent to prison *as a punishment* and not *for punishment*.[2] As you have stated, many youths wait for two months in local prisons before reaching reception centres. It might usefully be pointed out that, because of the rapidly changing population, the cell blocks in which they are housed (e.g., at Wormwood Scrubs) are actually in a worse state than those housing the more permanent adult prisoners. The stench of urine in these blocks is overpowering. It is a sorry thing that those in authority are apparently as impervious to these facts as the prison walls to the heat of a summer's day.

Yale University School of Medicine, New Haven, Connecticut. DENIS ABELSON.

1. *Proc. R. Soc. Med.* 1954, **47**, 632.
2. Prisons and Borstals. H.M. Stationery Office, 1957.

HIRSUTISM AFTER ADRENALECTOMY

SIR,—I was very interested in the report by Professor Bruce and his colleagues (Dec. 12), who noted vigorous facial hair growth after bilateral adrenalectomy and gonadectomy.

Thomas and I, in a study of some 600 patients,[1] found an increase in facial hair growth and disappearance of hair from the lower abdomen with advancing years. Gallwey and I, in a further unpublished study of about 400 patients, confirmed this and found a similar disappearance of hair at eight other sites. Clearly facial hair behaves differently from hair elsewhere after the menopause; some factor peculiar to this area must be presumed. The observations of Strong, Bruce, and Falconer suggest that this is non-hormonal, though a release from hormonal influence may be involved.

North Middlesex Hospital,
London, N.18. DAVID FERRIMAN.

TREATMENT OF INOPERABLE CANCER WITH 5-FLUOROURACIL AND IRRADIATION

SIR,—Curreri et al.[2 3] have shown that the administration of 5-fluorouracil, a pyrimidine antagonist, produces significant objective improvement in an impressive number of patients with far-advanced metastatic neoplastic disease.

1. Thomas, P. K., Ferriman, D. G. *Amer. J. phys. Anthrop.* 1957, **15**, 171.
2. Curreri, A. R., Ansfield, F. J., McIver, F. A., Waisman, H. A., Heidelberger, C. *Cancer Res.* 1958, **18**, 478.
3. Ansfield, F. J., Curreri, A. R. *J. nat. Cancer Inst.* 1959, **22**, 497.

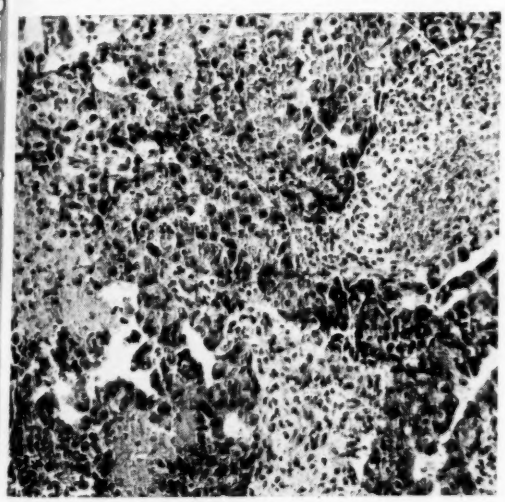

Fig. 1—Embryonal-cell carcinoma.

The most favourable results were in carcinoma of the breast, ovary, large bowel, and rectum, and in hepatoma. Variable responses were noted in a number of neoplasms, including carcinoma of the cervix. No response was obtained in carcinoma of the lung, stomach, pancreas, and kidney, and in a variety of other tumours, including embryonal-cell carcinoma of the testis. Tumour regression was observed only in patients treated to a toxic level. Toxicity was characterised by stomatitis and diarrhœa, and later by suppression of hæmatopoiesis, and severe toxicity by ulcerative lesions in the alimentary canal.

In the hope of avoiding moderate to severe toxicity, we decided to administer 5-fluorouracil in sub-toxic doses concomitantly with deep-ray therapy.

Initially, patients with inoperable carcinomas of the head and neck and of the lung were selected for combination therapy. Subsequently, other types of malignant disease have been treated by this means also. Treatment consisted of the intravenous administration of 5-fluorouracil throughout the period of irradiation, except in isolated instances when 5-fluorouracil therapy was discontinued temporarily because of manifestations of toxicity (stomatitis, diarrhœa, or leucopenia). The dosage was as follows: 15 mg. per kg. per day for 4 days, 7·5 mg. per kg. on the fifth day, and thereafter 7·5 mg. per kg. twice weekly until the course of irradiation had been completed.

In 3 patients with undifferentiated squamous-cell carcinoma of the lung, in 2 patients with pulmonary metastases secondary to embryonal-cell carcinoma of the testis and to adenocarcinoma of the rectum, and in 1 patient with lymphoepithelioma, 5-fluorouracil and X-ray therapy were stopped when a radiation (tumour) dose of 2000–2250r had been given. Chest films were taken before and two weeks after completion of therapy. All other patients in our series received larger doses of radiation than those mentioned above.

All the patients who received 2000r plus 5-fluorouracil showed rapid and significant regression of their lesions except for the patient with pulmonary metastases secondary to adenocarcinoma of the rectum. These observations suggest that either there may be an additive effect when the two treatments are used simultaneously or that one method may potentiate the anti-tumour effect of the other. Since 5-fluorouracil alone in carcinoma of the lung did not produce tumour regression in the cases of Curreri et al., and since a tumour dose of 2000r administered alone rarely produces a significant response in this type of tumour, it is possible that 5-fluorouracil actually increases tumour radiosensitivity.

To date, excellent initial responses to combined therapy have been observed in 6 of 8 squamous-cell carcinomas of the lung, in 4 of 5 squamous-cell carcinomas of the head and neck, and in 1 patient each with embryonal-cell carcinoma of the testis, adenocarcinoma of the breast, undifferentiated carcinoma (primary site unknown), and reticulum-cell sarcoma.

A man aged 23 years had a right orchidectomy and bilateral iliac and preaortic lymph-node dissections in March, 1958, for embryonal-cell carcinoma (fig. 1). This was followed by X-ray treatment to the retroperitoneal area during the spring of 1958. The patient was well until March, 1959, when chest pain, hæmoptysis, and exertional dyspnœa developed. A chest film revealed large bilateral pulmonary metastases (fig. 2a). An Ascheim-Zondek test was negative at 500 μ per litre. Urinary 17-ketosteroids were 9·0 mg. per 24 hours and 11-hydroxysteroids 5·0 mg. per 24 hours. Combined treatment was begun on April 13 and completed on April 28 (2000r, esti-

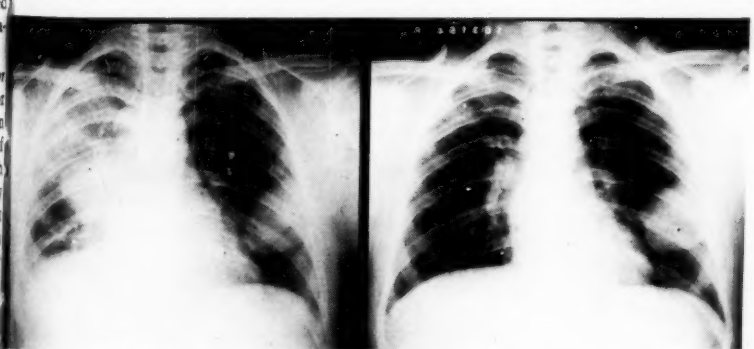

Fig. 2—(a) Chest radiograph before combined treatment (March 20); (b) after treatment (May 12) with 5-fluorouracil and irradiation of right hilar mass.

mated tumour dose to the right hilar mass, plus 6170 mg. of 5-fluorouracil). The irradiated metastatic lesion in the right hilum regressed (fig. 2b), but the non-irradiated lesion in the left lung did not.

Obviously, long-term studies with large numbers of cases will be necessary before a definitive evaluation of combined therapy versus irradiation alone can be attempted.

We wish to thank Hoffmann-LaRoche, Inc., Nutley, N. J., and the Cancer Chemotherapy National Service Centre for generously supplying 5-fluorouracil for this study. This study was supported in part by grants-in-aid from the National Cancer Institute, United States Department of Health, Education and Welfare.

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ALCOHOLISM AND HEPATIC CIRRHOSIS

SIR,—Your report (Dec. 12) of the meeting on alcoholism and cirrhosis of the liver, held in New York, mentions estimates that ". . . one in sixteen of those who take alcohol becomes an alcoholic and about 8% of these will develop cirrhosis". Figures of 8% or 9% are usually quoted, however, as the proportion among "chronic alcoholics" who develop cirrhosis,[1 2] and by no means all alcoholics show the bodily and mental disorders which according to the definition of Haggard and Jellinek [1] and the W.H.O. alcoholism subcommittee [3] denote "chronic alcoholism". For example, the proportion of "chronic alcoholics" among all alcoholics in the United States, according to Jellinek's latest estimates, is less than 20%.[2] According to the W.H.O. subcommittee, the term "alcoholics" includes not only those excessive drinkers who show "an interference with their bodily and mental health" but also those in whom drinking interferes with "their interpersonal relations and their smooth social and economic functioning", and those "who show the prodromal signs of such developments".[4] Thus much less than 8% of all alcoholics can be expected to develop liver cirrhosis.

As the figures of 8% or 9% refer to the incidence of alcoholic cirrhosis of the liver (among alcoholics with complications) relative to other complications of alcoholism, a decrease of other complications would automatically increase the relative incidence of liver cirrhosis among chronic alcoholics. In North America, because of a considerable fall between 1943 and 1950, in the incidence of alcoholic polyneuropathy and of certain other complications, the relative incidence of liver cirrhosis among alcoholics with complications is now estimated by Jellinek as amounting to 14% or 16%. Jellinek states, however, that these changes in the relative incidence of alcoholic complications have not occurred in Europe.[2]

Much more common, of course, in alcoholics than liver cirrhosis is fatty infiltration of the liver.[1] It seems that in this country the great majority of alcoholics entering mental hospitals which take a special interest in alcoholism hardly ever show clinical evidence of liver damage. Such people often show abnormalities when investigated with a battery of liver-function tests.[5] After a period of abstinence and a balanced vitamin-supplemented diet such laboratory abnormalities often prove reversible, thus corresponding to the improvement noted in your report.

1. Haggard, H. W., Jellinek, E. M. Alcohol Explored; pp. 177, 182, 189. New York, 1950.
2. Jellinek, E. M. *Quart. J. Stud. Alc.* 1959, **20**, 261.
3. *World Hlth Org. techn. Rep. Ser.* 1951, **42**, 19.
4. *ibid.* 1952, **48**, 16.
5. Kay, W. W., Murfitt, K. C., Glatt, M. M. *J. ment. Sc.* 1959, **105**, 748.

Liver cirrhosis is a very important complication of alcoholism, but it must not be forgotten that it occurs in a relatively small minority of alcoholics only, and in these at a relatively late stage of their alcoholic career. In view of the deterioration of judgment and performance with even small quantities of alcohol,[6] it is not surprising that a great many alcoholics show evidence of behaviour disturbance long before they enter their "chronic phase" and possibly develop liver cirrhosis.[7] The W.H.O. expert committee on alcohol and alcoholism has pointed out that "while the physical and mental sequelæ of alcoholism have always been recognised as medical disorders, there has been . . much less readiness to regard as matter of medical concern the behaviour which results in these complications".[8] At present many alcoholics are not recognised as such till they have arrived at their late "chronic" stages. Medical education on alcoholism, therefore, should not be exclusively or even predominantly concerned with the teaching of late complications but should lay due emphasis on the much more common and earlier disorders of conduct. The teaching of medical students will then further contribute to the aim so rightly stressed in your report that "every effort should be made both to secure early diagnosis . . . and to ensure continued abstinence".

St. Bernard's Hospital, Southall, Middlesex. M. M. GLATT.

THE COST OF DRUG TREATMENT

SIR,—It is to be hoped that the departments of the Ministry of Health concerned with prescribing and its cost to the N.H.S. will ponder well the revealing article by Dr. Miller and Dr. Smith (Jan. 2). They rightly draw attention to the paradoxical economics of general practitioner prescribing with especial relation to long-term saving of inpatient costs and national productivity by the use of some of the more expensive drugs in general practice.

Over the head of every N.H.S. practitioner hangs the spectre of a prescribing investigation with the possible (but very uncommon) consequence of deduction from his quarterly cheque of the cost of certain drugs considered necessary by him for his patients but not, apparently, by the powers that be. These inquiries follow periods of full pricing of all prescriptions by the executive councils at intervals in each year. In any case, local pharmacists will know in advance when "pricing" will be in operation and can warn doctors beforehand.

As I have pointed out previously,[9] little or no attempt is made by drug manufacturers to inform doctors of the total cost to the N.H.S. of their products. The basic cost represents an artificial and in some cases minute proportion of the total cost of a prescription, as Dr. Miller and Dr. Smith have noted, and has a much more attractive appearance on advertising literature.

Most of us suffer from the rapacity of patients, and all of us realise that refusal to prescribe a substance demanded by a patient against our better judgment may possibly lead to his transfer to another doctor who will prescribe it regularly with a clear conscience, with resulting loss of capitation fees to ourselves. I wonder how many practices have been built up by high prescribing relative to neighbouring doctors at the expense of the national drug bill. Complaisant negligence by doctors is perhaps a subconscious defence mechanism to safeguard our incomes. To achieve a balance in this respect is one of the most disturbing aspects of practice to some of us who work in areas where standards of living are increasing.

London, N.W.2. D. S. NACHSHEN.

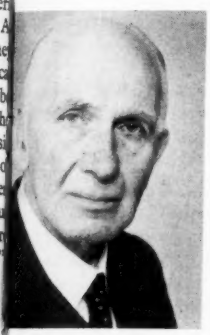
6. See *Lancet*, 1960, i, 41.
7. *World Hlth Org. techn. Rep. Ser.* 1952, **48**, 29.
8. *ibid.* 1955, **94**, 3.
9. *Brit. med. J.* 1959, ii, suppl. p. 20.

Obituary

WILLIAM ERRINGTON HUME

Kt., C.M.G., M.A., M.D. Cantab., F.R.C.P.

Sir William Hume's early election to the staff of the Royal Victoria Infirmary gave him an unusually effective working span, but its length was appropriate to the work which he accomplished. The Newcastle medical school valued his contribution as a pioneer of scientific medicine, an outstanding teacher, and an upright man. He died on Jan. 1 at the age of 80.



His father, George Haliburton Hume, practised as a surgeon in Newcastle upon Tyne and took a large part in the building of the Royal Victoria Infirmary. Hume himself was educated at Repton School and Pembroke College, Cambridge. At the London Hospital he was clerk to Sir Bertrand Dawson, and after qualifying in 1904 he returned to Newcastle to hold a succession of resident appointments. He was senior house-physician at the Royal Victoria Infirmary when it moved into its new buildings in 1906. Two years later he was elected to the staff and was also appointed demonstrator in pathology at Durham University. From the first he was a brilliant teacher and his ward rounds and museum classes were always packed.

When the war began in 1914 Hume, by virtue of his hospital appointment, became a lieut.-colonel in the 1st Northern General Hospital; but he was anxious to serve abroad and joined a casualty-clearing station though this meant a loss of rank. Soon afterward he was posted to Boulogne, where he joined his old chief Dawson in the organisation of centres for cases of D.A.H. They also began an investigation into spirochætal jaundice, which S. P. Bedson was invited to join. He writes:

"Hume and Dawson were interested in the cases of Weil's disease which were occurring in our troops in the wet trenches of Flanders, and Hume, knowing that I had been unable to obtain suitable war work, suggested to Dawson that it might be possible to have me transferred to them and made responsible for the laboratory side of their investigations. This was arranged and I joined them to spend three most pleasant and valuable years working with them. Hume and I were billeted together in Wimereux near to the house in which I had installed my laboratory and next door to Lord Dawson and to a refugee French family from Lille. Friendship with our French neighbours prospered and much of our leisure was spent enjoying the delightful hospitality of Madame Tisseyre and her family; Hume later married the elder daughter. Not only did I find Hume a most valuable colleague, but he proved also to be a delightful companion. He was entirely unselfish, had a real sense of humour, was not inappreciative of the good things of life and was withal of a complete integrity. The time spent in his company was the basis of a friendship which I shall always cherish."

Before the end of the war Hume was appointed consulting physician to the 1st Army, and for this work and his research on poison gas he was mentioned in despatches and received the C.M.G. After his return to civilian practice his papers on war nephritis and encephalitis lethargica were useful continuations of his work during these war years. But his chief interest lay of course in cardiology. Early in his days at Newcastle he studied intensively the heart rhythm in diphtheria. As early as 1913 he had described what is now called auricular flutter, and as the subject of his Bradshaw lectures in 1917 to the Royal College of Physicians of London he chose paroxysmal tachycardia.

He was elected F.R.C.P. that year, and later he served the college as censor and as senior censor in 1941. In 1943 he gave a war-time Harveian oration with the appropriate title of "the physician in war in Harvey's time and after". In 1943 he had been appointed to the chair of medicine at Newcastle, but in 1940 on his retirement from his hospital appointment he resigned.

For some years he remained on the staff of the Newcastle General Hospital, and he was largely responsible for setting up the regional cardiovascular centre. He gave much other counsel to the organisation of the services of the region in the early days of the National Health Service. He was knighted in 1952, the year when increasing ill health finally forced him to retire from practice.

H. G. M. recalls the advice he received when he became Dr. Hume's house-physician in 1938: "Have every patient electrocardiographed, and always carry twenty 'Gold Flake' in your pocket."

"Hume (he continues) was a superb clinician, and the contrast between his astute empiricism and the more speculative approach of his assistant physician, James Spence, was a rewarding and sometimes diverting experience.

"Hume held the chair of medicine largely by virtue of his clinical seniority. Such a procedure would be unthinkable today, but in retrospect it furnished here and elsewhere a cadre of clinical professors many of whom yield nothing in eminence or achievement to their successors appointed on other grounds. Of such was William Hume, a man of extraordinary mental acuteness, with no time whatever for cant or pretence, able to diagnose a humbug with the same instantaneous flair as he did auricular flutter. His systematic lectures were unforgettable. As he entered the theatre he peppered members of the audience with searching questions based on the subject-matter of the previous meeting. These lectures represented the essence of a vast personal experience, sifted by unflagging and meticulous observation. He never used a note or quoted an authority, but he always had an appropriate clinical anecdote at his fingertips, drawn from his war-time service in France, his experience as an outstanding witness in the courts, or his daily work as a busy and successful consultant physician in the colliery villages and great houses of Northumberland and Durham.

"One of a generation of great general physicians, many of whom were his close friends, Hume nevertheless encouraged genuine specialisation, particularly in his own interest of cardiology. He maintained however an amused contempt for some of the more recent synthetic specialties, and for what he regarded as the essential triviality of much that currently passes for research.

"He lived and breathed medicine. His great delight was fishing, but even when he went up for a few days on the Border, a couple of beds were always kept empty for the cases, whether of heart-block, cerebral tumour, or obscure pyrexia, that were sure to be 'rung in' from Wooler or further north. He retained this vivid interest in medicine until the end. Only a few weeks ago he summoned me to his home by a peremptory telephone-call to discuss and criticise a paper in preparation, about which he had heard in the course of the medical gossip with which he always loved to surround himself.

"Truth to tell—and although he was never anything but kind—I think we were all just a little frightened of him. His juniors' only consolation was that Knowledge and Wisdom so palpably superior, though so lightly worn, seemed to be not without a slightly intimidating effect on many of his near-contemporaries."

Lord Moran writes:

"I think of William Hume with Dawson and Wilmot Herringham as central figures of another time. Consulting

physician to the British Forces in France in the First War, he was Dawson's right-hand man at Boulogne, and Herringham, who was inclined to be impatient with mediocrity, thought well of him. After the war, Hume was one of the three founders of the Cardiac Club, where he was well liked as a keen, cheerful, and kindly man. And John Parkinson has said that when they met he felt invigorated. It is now a quarter of a century since he was a councillor at the College, having already given the Bradshaw lecture; soon he became a censor and a little later gave the Harveian oration. I read what he wrote, for it was salted by horse-sense and always to the point. Besides, he had the literary art.

"About William Hume there was an air of distinction. Moreover he was a master of his craft. I think of him as among the two or three physicians in the Provinces whom I most wished visitors to England to meet. He was a brave soul; though he had to contend with years of pain and crippling illness, it never seemed to get him down. Lately he was so much in pain, so frail, and so weak that I used to telephone when I was in Newcastle to find whether he felt equal to a visitor. But he was always ready to talk on anything save his own illness, and he never lost his healthy outlook. I can only guess what he owed to the wisdom and understanding of his wife.

"William Hume was a considerable figure in the North of England and I count him in the direct line of descent from those English physicians who, proficient in their art, were also men of affairs, the kind of men who had influence beyond their own calling."

Sir William Hume is survived by his wife, three daughters, and two sons. One of his sons is in practice in Sunderland, and his eldest daughter is married to Sir John Charles.

JOHN ERNEST ALFRED UNDERWOOD

C.B.E., M.B., B.Sc. Lond., D.P.H.

Dr. J. E. A. Underwood, a former principal medical officer of the Ministry of Education, died suddenly on Dec. 31, at the age of 73.

The son of Ernest Underwood, of Blackheath, he was educated at Blackheath School, University College, London, where he was president of the Union, and University College Hospital. He graduated B.Sc. in 1910 and qualified in 1915, when he joined the R.A.M.C., serving in France and India. On his return to civilian life he took the M.B. and the D.P.H., and in 1921 he became medical officer of health and school medical officer for Willesden. He joined the staff of the Board of Education in 1925 and succeeded Dr. J. A. Glover as principal medical officer in 1941. He was appointed C.B.E. in 1948 and retired in 1951.

Underwood was particularly interested in the problems of children who were blind or deaf, and he represented the Government at the international conference on the welfare of the blind held in New York, in 1931. He was secretary of the Committee on Partially Sighted Children that reported in 1934, and was vice-chairman of the one set up in the same year to inquire into problems relating to children with defective hearing. In his later years at the Ministry of Education he became increasingly concerned with emotionally disturbed children, and when the Committee on Maladjusted Children was appointed in 1950 he was made chairman. The work of this committee occupied much of his time during the first years of his retirement. The committee's main recommendations were accepted by the Government and were the subject of recent circulars from the Ministries of Education and Health on the development of child-guidance services. From early in his retirement he was a member of the governing bodies of Moor House School for Children with Speech Defect, Oxted, and the Heritage Craft Schools and Hospitals, Chailey, and also of the Mid-Sussex hospital management committee.

A colleague writes:

"Underwood read widely and he had a good collection of books. His presidential address to the Medical Officers of Schools Association was a scholarly review of the allusions to medicine in the works of Shakespeare. He enjoyed foreign travel. He was somewhat reserved in manner but to those who knew him well he was an excellent companion, with a nice but never malicious, wit and a great depth of common sense. He was never known to lose his temper and was tolerant to a degree that sometimes became embarrassing.

"On the day of his death, as was his custom, he went for an afternoon walk with his collie dog across the fields near his home in Sussex. When darkness came down and he did not return a search party went out, but his body was not found until next morning: he lay in the field where he collapsed, guarded by his dog who, at first, fiercely resisted the searchers."

Dr. Underwood is survived by his widow, Catherine German, whom he married in 1923.

JOHN RITCHIE

M.B. Edin., F.R.C.P.E., D.P.H.

Dr. John Ritchie, formerly medical officer of health for Dumfriesshire, died in Edinburgh on Dec. 24.

Born and educated at Brechin, Angus, he qualified from Edinburgh University in 1906 and took the D.P.H. the following year. After holding appointments in the City Hospital, Edinburgh, as resident, senior assistant, and bacteriologist, he was appointed depute medical officer of health and bacteriologist to the County of Dumfries where he spent the rest of his career. He became M.O.H. in 1924 and he retired in 1947.

In 1935 he was appointed to the General Medical Council as Crown nominee for Scotland and he held this appointment for ten years, serving also as chairman of the Council's public-health committee from 1939 to 1945. He was a member of the National Insurance Advisory Committee from 1947 to 1952.

He retired to Edinburgh in 1947 and was soon taking an active part in the medical affairs of the city, especially in the Royal College of Physicians. He became superintendent of the College laboratory in 1948 and was the last of a long line of distinguished superintendents, for the activities of the laboratory ceased in 1950. Later he was honorary librarian of the College, a position from which he only recently resigned. He had a deep interest in medical history and made many contributions to the subject, including a history of the laboratory of the College. He was a founder member of the Scottish Society of the History of Medicine, serving as its president from 1951 to 1954.

A colleague writes:

"No more will we see the familiar erect figure of Dr. Ritchie in the precincts of the College of Physicians or of the many libraries which were the great centres of his interest after he retired to Edinburgh. He was a prodigious worker resembling in many respects Osler of whom he was a keen admirer. A copious note-taker, all items which interested him were entered into his commonplace books and all carefully indexed. Thus it was that his contributions to medical and medico-historical literature were fully documented and appropriately illustrated by well-chosen examples. In his earlier years he had thought of becoming a naval architect, and he had a keen appreciation of art. His letters and reports were often enlivened by the artistic touch, and by the fitting phrase for he was a man of wide reading and culture. He had, too, a great gift for short-story writing, mainly in lighter vein, and contributed to various magazines. For all his accomplishments and ability, he was a quiet self-effacing man who loved the intimacy of the family circle and deliberately shunned the public eye."

CEDRIC SYDNEY LANE-ROBERTS

C.V.O., M.S. Lond., F.R.C.S., F.R.C.O.G.

Mr. Cedric Lane-Roberts, consulting obstetrical surgeon to Queen Charlotte's Hospital and consulting gynæcological surgeon to the Royal Northern Hospital, London, died on Dec. 25 at the age of 71.

He was the third son of the late Lieut.-Colonel A. S. Roberts and he was educated at Cheltenham College and Guy's Hospital where he was distinguished as a medallist and as a rugby player. He qualified in 1913 and was mentioned in despatches for his service in the R.A.M.C. during the 1914–18 war. After demobilisation he held for a time the appointment of tutor in obstetrics and resident medical officer at Leeds Maternity Hospital. In 1920 he took the M.S. and the F.R.C.S., and soon afterwards he returned to London on his appointment as chief assistant in the women's department and obstetric tutor at St. Bartholomew's Hospital. Later he was appointed to the staffs of Queen Charlotte's Hospital and the Royal Northern Hospital and he also built up a large consultant practice. He contributed to the *Royal Northern Operative Surgery* and the *Queen Charlotte's Practice of Obstetrics*. He was joint author of *Sterility and Impaired Fertility*.

He was a foundation member of the Royal College of Obstetricians and Gynæcologists and he was elected to the fellowship in 1933. He was appointed C.V.O. in 1942.

K. W. writes:

"*Who's Who* tells you the facts about Lane-Roberts, his hospital appointments and that he played in the English Rugby Football team four times and in the Guy's Hospital team for six years, but the real Cedric Lane-Roberts, the big-hearted colleague with whom it was impossible to quarrel, is not revealed. He was undoubtedly a big, heavyweight bustling international forward, but he was big in many other fields than rugby football. Never have I worked with a colleague so loyal and dependable as he, and I saw a great deal of him at the Royal Northern Hospital. We were both interested in the subject of human fertility and having secured some funds from what is now the Beecham Trust we were able to establish there one of London's earliest parenthood clinics. But again I am giving a lopsided account of a man who had many interests outside his professional work. One was always unearthing unexpected hobbies in him: Greek architecture, ancient Chinese bronzes and lacquer work, Tibetan pictures of the Buddha, and, more prized than all these—his garden at the Mill House, Tewin."

Mr. Lane-Roberts married Nell Miles-Sharp, daughter of the late D. W. Bain, and she died in 1954.

Public Health

Infectious Diseases in England and Wales

Disease	Week ended December 5	12	19	26*
Diphtheria	5	17	7	2
Dysentery	723	803	910	683
Encephalitis:				
Infective	1	1	3	5
Postinfectious	..	3	1	..
Food-poisoning	190	193	377	164
Measles, excluding rubella	1113	1128	1083	948
Meningococcal infection	26	16	20	14
Ophthalmia neonatorum	20	12	28	8
Paratyphoid fever	1	1	3	4
Pneumonia, primary or influenzal	305	324	325	233
Poliomyelitis:				
Paralytic	11	5	4	1
Non-paralytic	2	2	..	1
Puerperal pyrexia	156	189	174	125
Scarlet fever	1418	1537	1333	1001
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	432	434	400	262
Meninges and C.N.S.	6	4	1	6
Other	44	48	42	25
Typhoid fever	3	2	2	1
Whooping-cough	739	672	561	371

* Not including late returns.

Notes and News

A COLLEGE BILL

In the life of an institution, a family, or an individual, a flitting is an opportunity for repair, replacement, and renovation. In preparation for its move from Pall Mall East to Regent's Park, the Royal College of Physicians is presenting a Private Bill to Parliament to modify and clarify some of its ancient rights.

The first, though not perhaps the most important clause of the Bill, proposes that the college shall be called and known as "The Royal College of Physicians of London". This title is already familiar by usage and repute. But in the original royal charter, granted in 1518 by King Henry VIII, the college is described as "The President and College or Commonalty of the Faculty of Physic in London", and it may be that this pleasant, if cumbersome, name is the only one it has actually been authorised to use. Though the familiar form stands in the Medical Acts since 1958 the archaic form has been retained in most of the college's legal documents, including those drawn up when it moved to Pall Mall East from the City.

The second clause of the new Bill deals with another difficulty which the college first met at the time of this earlier removal. Under the original charter it was only empowered to hold its meetings in the City of London, and when it moved to Westminster powers had to be obtained to allow it to act there. Under the new Bill, its territorial choice would be extended to the whole of England.

A third clause removes a limitation imposed by the Act of 1814, which only allows the college to hold lands of an annual value not exceeding £1000 a year, a ceiling which changing values has unfortunately made unsuitable.

TWO-YEAR MEDICAL SCHOOLS

In the past twelve years the John and Mary R. Markle Foundation has taken a special interest in the support of young doctors planning careers in teaching and research at medical schools in the United States and Canada. In the latest annual report Mr. John M. Russell, executive director, cites the Bayne-Jones report to the Department of Health, Education, and Welfare, which suggests that in the next ten years at least 1900 additional doctors will have to be trained. One of the ways proposed for training them is to increase the number of "two-year" medical schools, which cover the first two years of the medical course and send their students elsewhere for clinical work.

In several of the large American cities the medical schools have clinical facilities not fully utilised and could handle more students, while "some colleges", Mr. Russell says, "have excellent departments in the life sciences which could be expanded without great expense into a two-year medical course". Professors at these colleges may be reluctant for several good reasons: "a medical school, next to the football team, can cause the most headaches in any university", and they fear that the additional tasks may mean more teaching and less research. While agreeing that basic research must be protected at all costs, Mr. Russell feels that the attitude toward teaching is another matter:

"The lack of interest in teaching undergraduates in American institutions with graduate schools is a curious phenomenon and seems to stem from the methods used to climb the academic ladder. To get a promotion or a new job, to get tenure and more pay, it is important to publish, and to publish requires research. There is, in fact, little incentive to teach. However, at the graduate level teaching is favored. Graduate students are involved with research, and the research usually is in the particular area of interest of the professor." Hence "the reluctant professors should not be taken too seriously. . . . Teaching does have its satisfactions and there are ways in which the teacher can be recognized with pay, rank and tenure, while at the same time protecting his time for research."

The Foundation has distributed nearly 5½ million dollars since it was established in 1927. Its address is 511, Fifth Avenue, New York City, 17.

Hellingly Hospital, Sussex

Last July the first patients were taken into the new 60-bed unit for the investigation and treatment of early psychiatric illness which has been built for Hellingly Hospital (near Hailsham) two miles from the main building. It is called Amberstone Hospital, and patients are admitted on the recommendation of any member of the Hellingly consultant psychiatric staff. Instead of having an official opening, Dr. David Rice (the medical superintendent) and his colleagues have held open days for the doctors of the neighbourhood, who were invited to meet the senior staff, discuss any subject in which they were interested, and see demonstrations of electroconvulsion therapy.

The unit will take 35 female and 25 male patients. Accommodation is in single rooms or in curtained cubicles in the 4-bed and 8-bed dormitories. The staff is mixed: one shift has a sister in charge (with a male staff nurse as second in charge) while the other shift has a charge male nurse with a female staff nurse as his first assistant.

University of Liverpool

On Wednesday, Jan. 20, at 8 P.M., at the Medical School, Ashton Street, Liverpool, Dr. W. H. Taylor will give the first of eight weekly lectures on biochemical aspects of disease. Tickets (£2 2*s*.) may be had from the director of extramural studies, 9, Abercromby Square, Liverpool, 7.

University of London

Dr. D. R. Newth, lecturer at University College, has been appointed to the chair of biology as applied to medicine at Middlesex Hospital Medical School.

The degree of M.S. has been conferred on Gerald Keen.

University of Glasgow

Dr. W. M. Gibson has been appointed to the chair of dental prosthetics.

Royal Statistical Society

Frances Wood Prize (*£50*).—This prize is offered for an investigation, on statistical lines, of any problem which bears "directly or indirectly upon economic or social conditions". Competitors must be under 35. Further particulars may be had from the honorary secretaries of the society, 21, Bentinck Street, London, W.1. The closing date for entries is Dec. 31.

James Yearsley Lecture

Mr. Ian Thorburn will deliver this lecture on Friday, March 4, at 5 P.M., at 1, Wimpole Street, London, W.1. His subject will be tympanoplastic surgery.

Anglo-French Exchange Bursaries

Short-term grants for work in France are offered again this year to British doctors and medical research workers by the Institut National d'Hygiene, Paris. Details and application forms can be had from Dr. G. E. W. Wolstenholme, Ciba Foundation, 41, Portland Place, London, W.1. The closing date is Jan. 31.

Appeal to the Privy Council

Dr. Kenneth Fox has lodged an appeal with the Judicial Committee of the Privy Council against the decision of the Disciplinary Committee of the General Medical Council to erase his name from the register.

Dr. D. A. Buxton Hopkin, consultant anæsthetist at Charing Cross Hospital, London, has been appointed the first McDermott visiting professor of anesthesiology in the University of Texas. The appointment is for one year and Dr. Buxton Hopkin expects to take up the post early in April.

On Wednesday, Jan. 13, at 5.30 P.M., at the Fountain Hospital, Tooting Grove, London, S.W.17, Prof. L. S. Penrose and Dr. P. E. Polani will speak on chromosomal abnormalities in the mentally retarded.

At the request of the Government of Pakistan the British Government, under the auspices of the Colombo Plan, have asked Prof. Charles Wells and Prof. H. P. Gilding, as members of a Pakistan Commission, to report on the health services organisation in Pakistan. They leave in January for a tour of three months.

Diary of the Week

JAN. 10 TO 16

Tuesday, 12th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. F. Ray Bettley: Effects of Soap on the Skin. (Watson Smith lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry*. Dr. W. Grey Walter, Dr. W. Ross Ashby, Prof. H. Eysenck: Conditioning Theories and Their Therapeutic Applications.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. J. H. Dible: Pathology of Limb Ischæmia.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Claude Taylor: Malignant Disease of the Uterus.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. F. Swann: Plain X-ray Changes in the Skull.

MANCHESTER MEDICAL SOCIETY
8 P.M. (Clinical Sciences Building, York Place, Manchester.) *Surgery*. Prof. A. M. Boyd: Self-inflicted Injuries.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Mr. T. P. S. Powell: Cortical Representation of Somatic Sensation.

Wednesday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Dr. P. L. Mollison: Destruction of Red Cells by Immunological Mechanisms.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Arthur Tickner: Serum Proteins in Skin Disease.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. E. H. Hudson: The Changing Face of Chest Disease.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh.) Lord Kilbrandon: Common Interests.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow
5 P.M. Sir Gordon Gordon-Taylor: Mars and Æsculapius. (Fleming lecture.)

Thursday, 14th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Prof. J. W. Crofton: Tuberculosis Undefeated. (Marc Daniels lecture.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Sir Walter Mercer: Some Edinburgh Pioneers in Orthopædic Surgery. (Robert Jones lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. H. L. Sheehan: Infarction.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. L. Forman: Cutaneous Manifestations of Visceral Malignancy.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. H. J. G. Bloom, Mr. D. M. Wallace, Mr. Robert Cox: Treatment of Carcinoma of the Bladder.

ALFRED ADLER MEDICAL SOCIETY
8 P.M. (1, Wimpole Street, W.1.) Dr. Walter Schindler: Indications for Group Psychotherapy.

Friday, 15th

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine*. Dr. N. S. Galbraith, Dr. J. C. McDonald, Flight-Lieutenant D. M. Miller, Dr. M. Patricia Jevons, Dr. J. D. Rycroft, Dr. R. E. O. Williams: Carriers of Penicillin-resistant Staphylococci Outside Hospital.
8.15 P.M. *Radiology*. Dr. J. G. Stewart, Dr. Robert Gibb, Dr. K. S. Holmes, Dr. R. C. S. Pointon: Clinical Applications of Megavoltage.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. R. W. Raven: Cancer Cell and Surgery.
4 P.M. Dr. J. F. Goodwin: Pulmonary Circulation in Heart-disease.

FACULTY OF RADIOLOGISTS, 47, Lincoln's Inn Fields, W.C.2
4.30 P.M. (Royal College of Surgeons.) *Radiotherapy*. Dr. J. S. Fulton, Dr. Richard Doll, Dr. F. Dudley Hart: A Critical Survey of the Value of Radiotherapy in the Treatment of Ankylosing Spondylitis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. Maxwell Ellis: Nasal Physiology and Pathology.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.30 P.M. Dr. P. K. Thomas: Clinical Applications of Electromyography.

PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Mr. R. V. Cooke: Bees in my Bonnet.

Appointments

BARTON, R. W. A. C., M.B. Lond., D.P.M.: physician-superintendent, Severalls Hospital, Colchester, Essex.

CROSS, R. M. S., M.R.C.S.: ophthalmologist (S.H.M.O.), Petersfield school eye clinic.

DANIK, J. J., Dipl. Lwow, D.P.M.: consultant psychiatrist, Towers Hospital, Humberstone, Leicester.

PLATT, J. W., B.M. Oxon., M.R.C.P., D.C.H.: consultant pædiatrician, Cumberland and North Westmorland area hospitals.

STRAUSS, W. T., M.D. Hamburg, F.R.F.P.S.: consultant physician, Arbroath Infirmary and Dundee Royal Infirmary.

Manchester Regional Hospital Board:

CROSS, J. R., M.B. Birm., F.F.A. R.C.S.: part-time consultant anæsthetist, South Cheshire group of hospitals.

HALNAN, K. E., M.D. Cantab., F.F.R., D.M.R.T.: consultant radiotherapist, Christie Hospital and Holt Radium Institute, Manchester.

ROGERS, VINCENT, M.B. Lpool, D.M.R.D.: part-time consultant radiologist, Salford group of hospitals.

SMITH, H. F., M.B. Manc., F.R.C.S.: consultant surgeon, Blackpool and Fylde group of hospitals.